DELAYED REWARD DISCOUNTING AS AN ENDOPHENOTYPE FOR PATHOLOGICAL GAMBLING

by

JOSHUA CHARLES GRAY

(Under the direction of James MacKillop)

ABSTRACT

This study used an endophenotype approach to examine if delayed reward discounting (DRD; i.e., a behavioral economic index of impulsivity) clarifies associations between a panel of dopaminergic (DA) single nucleotide polymorphisms (SNPs) and pathological gambling (PG) in a sample of frequent gamblers of European ancestry (N = 175). In *a priori* tests, two loci previously associated with DRD (rs1800497 and rs4680) were not replicated, although significant associations were present in five genomically proximal loci. Exploratory analysis of 153 loci in genes related to DA neurotransmission revealed six additional significant associations, three in *SLC18A2* and one in *DRD5*, *DRD1*, and *DDC*. Notably, an aggregate genetic risk score, generated from the 11 significantly associated SNPs, was significantly associated with PG severity and this relationship was fully mediated by their relation with DRD. This finding provides further evidence of genetic influences on DRD and preliminary support of DRD as an endophenotype for PG.

INDEX WORDS: Pathological Gambling; Delayed Discounting; Genetics; Endophenotype

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DEDICATION

To Ryan.

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CHAPTER 1

INTRODUCTION

Pathological gambling (PG) is a prominent public health problem in modern day society. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) defines PG as a “persistent and maladaptive gambling behavior” indicated by at least five of ten symptoms that are comparable to symptoms of substance dependence (i.e., high severity and compulsivity of behavior) and substance abuse (i.e., experience numerous negative consequences associated with behavior). Most of adults (78.4%) in the United States have gambled at least once in their lives, and a minority goes on to develop lifetime disordered gambling (2.3%; DG; one or more symptoms of PG) or PG (0.6%; five or more symptoms) (Kessler et al., 2008). As gambling has become more and more accessible in western society, rates of PG have been growing (Wardle, Griffiths, Orford, Moody, & Volberg, 2012). Comorbidity between PG and other psychiatric disorders is very high, especially for alcohol use disorder (73.2%), drug use disorders (38.1%), nicotine dependence (60.4%), mood disorders (50%), anxiety disorders (41%), and personality disorders (61%) (Petry, Stinson, & Grant, 2005). Furthermore, a cross-sectional study examining age of onset of psychological disorders found PG to be associated with the subsequent development of substance use disorders (SUDs) (Kessler et al., 2008). Pathological gambling has a substantial impact on communities as it is associated with criminal behavior, bankruptcies, divorce, child abuse and neglect, and suicide by problem gamblers and their spouses (Goodman, 1994; Lesieur, Henry & Anderson, 1995; Petry & Kiluk, 2002; Shaw, Forbush, Schlinder, Rosenman, & Black, 2007; Thompson, Gazel, & Rickman, 1996).

Etiology of Pathological Gambling

There is substantial evidence that PG has a strong genetic basis. Preliminary evidence for the genetic component of PG comes from family studies demonstrating that, in clinical samples of pathological gamblers, there is an incidence of about 20% of PG in first degree relatives (Lesieur, 1988; Ibanez & Saiz, 2000), a rate that is much higher than the general population prevalence. Additionally, numerous studies have found a higher frequency of DG and PG in subjects who perceived a problematic gambling behavior in their parents (Gambino, Fitzgerald, Shaffer, Renner, & Courtnage, 1993; Gupta & Derevensky, 1997, 1998; Lesieur & Heinman, 1988). These studies, of course, cannot address whether these increased rates are a function of environmental exposure.

Twin studies have been conducted to further discriminate the influence of common genetic factors, versus shared environmental and cultural factors. Considering concordance rates of the disorder in monozygotic versus dizygotic twins in shared environments helps to clarify specific genetic factors. Given the sharing of 100% of genetic variation in monozygotic (MZ) twins and 50% in dizygotic (DZ) twins, the difference in concordance of the pathology between the two twin types provides an estimation of overall genetic contribution. A summary of twin studies on genetic contributions to gambling behavior and PG status may be found on Table 1.

Three studies to date have looked at genetic influences on any participation in gambling behaviors. In an early study of 155 twins (41% female), Winters and Rich (1998) found that male MZ twins revealed a significantly greater similarity on gambling frequency associated with "high-action" games than DZ twins, but neither male nor female twins demonstrated differences in gambling frequency convergence in "low-action" games. Notably, these findings may be limited by the study's small sample size and the high base rate of the behavior. In a more

comprehensive recent study of 4,764 individuals from the Australian Twin Registry, Slutske et al. (2009) found that shared genetic factors explained 55% of the variance in lifetime involvement in any form of gambling. Most recently, Blanco, Myers, & Kendler (2012) examined 1,737 individuals in a web based sample and found that genetic factors accounted for approximately 32% of involvement in gambling.

In addition to studies of the genetic influences on gambling behavior in general, a number of studies have yielded compelling evidence for a strong genetic influence on PG behavior. In a study of 3,359 male twin pairs, it was determined that shared factors explained 62% of the variance in the diagnosis of PG disorder (Eisen et al., 1998). In an additional study, Slutske et al. (2000) found that the risk for PG was significantly higher among MZ (6.1%) and DZ (3.1%) co-twins of men with subclinical PG symptoms than co-twins of men with no PG symptoms, lending support that PG as a disorder is on a continuum with similar risk factors. Notably, in the web based study by Blanco et al. (2012), they found that in 1,739 individuals, genetic factors accounted for 83% of all variance in PG symptomatology and this result was invariant across genders. Furthermore, an additive genetic association with gambling problems of 72%, was identified in a population of 602 young adults and this was not found to differ by gender (Beaver et al., 2010). Additionally, in a follow-up study of PG symptoms in the Australian Twin Registry, no evidence was found for sex differences in the genetic causes of variation in liability (~51.8%) to PG symptoms regardless of the diagnostic measure used (i.e., National Opinion Research Center DSM-IV Screen for Gambling Problems (NODS) and South Oaks Gambling Screen (SOGS); Slutske, Zhu, Meier, & Martin, 2011). Interestingly a 10-year follow up study of the Vietnam Era Twin Registry examined the genetic architecture of lifetime PG and current PG symptoms and found no difference in genetic contributions to lifetime and past year gambling

symptoms 10 years later despite differential unique environmental influences (Xian et al., 2007). Overall, findings from these twin studies indicate that level of participation in gambling as well as PG symptomatology are strongly and robustly connected to genetic influences and these influences on PG are consistent overtime.

Candidate Genes for Conferring Risk for Pathological Gambling

A greater understanding of genetic contributions to PG could be used to identify those that are at the greatest risk for developing the disorder and develop new treatments that map onto differential constellations of genetic underpinnings of PG. Genetic contributions to addictive behaviors are thought, in part, to be due to the neurobiological variation in genes related to the reward, behavioral control and compulsivity, and stress response areas of the brain (Goldman, Oroszi, & Ducci, 2005). A summary of molecular genetic associations to PG, updated from Lobo and Kennedy (2009), can be found on Table 2.

Research on reduced reward sensitivity specific to pathological gamblers has found a blunted response in the ventral striatum in pathological gamblers (compared to controls) during monetary wins (Reuter et al., 2005). Reduced activity in regions associated with the mesolimbic reward center in pathological gamblers is consistent with the notion that these individuals are more driven toward highly stimulating activities (e.g., drugs and gambling) due to a hypoactive reward system. As such, numerous dopaminergic (DA) genes have been analyzed for associations between reward sensitivity and addictive disorders such as PG (Potenza et al., 2003). The TaqIA A1 allele of the dopamine receptor gene *DRD2* was initially associated with PG and other substance use and psychiatric disorders (Comings et al., 1996, 1997), however, a more recent study with more methodological rigors and controls failed to find differences in PG in relation to TaqIA A1 frequencies (da Silva Lobo et al., 2007). Notably, this relationship is

further complicated by the finding that the TaqIA marker is outside of the *DRD2* gene, located in a neighboring gene called ankyrin repeat and kinase domain containing-1 (*ANKK1*) (Neville, Johnstone, & Walton, 2004).

Two studies have focused on polymorphisms in the dopamine D_1 receptor gene (*DRD1*). A comorbid PG and alcohol dependence association to the homozygous *DRD1* (rs4532) A1 allele has been reported (Comings et al., 1997). Furthermore another study found an association with the T allele of a *DRD1* polymorphism (rs265981) in PG (da Silva Lobo et al., 2007). These associations with different polymorphisms in *DRD1* have been attributed to the high degree of linkage disequilibrium (LD), meaning these polymorphisms have been transmitted together throughout evolution with little interference from recombination processes.

Additionally, a variable number of tandem repeats (VNTR) polymorphism in exon III of the dopamine D4 receptor gene (*DRD4*) has been reported to encode a receptor that has a lower affinity for dopamine in multiple studies (Asghari et al., 1995; Jovanovic, Guan, & Van Tol, 1999; Van Tol et al., 1992). Two studies have found an association of the *DRD4* exon III polymorphism with PG, finding that overall long forms (i.e., five to seven repeats) were associated with PG status (Comings et al., 1999; Pérez de Castro, Ibáñez, Torres, Sáiz-Ruiz, & Fernández-Piqueras, 1997). However, in another study, this specific polymorphism was only associated with vulnerability to PG in females (Pérez de Castro et al., 1997). Notably, a recent case-control study of 104 PG and 114 age- and race-matched Korean males failed to replicate the relationship between any of the aforementioned DA genes and PG (Lim, Ha, Choi, Kang, & Shin, 2012).

Serotonergic alleles have been examined in two studies. The first found that the short version of the *5HTTLPR* polymorphism, associated with lower serotonin levels (Canli & Lesch,

2007), was associated with PG in males (Pérez de Castro, Ibáñez, Saiz-Ruiz, & Fernández-Piqueras, 1999). The second study, comparing 140 PG siblings with 140 non-PG full siblings, did not find an association between polymorphisms of *5HTTLPR, 5HT-1B*, and *5HT-2A* with PG status (Wilson, da Silva Lobo, Tavares, Gentil, & Vallada, 2013). Monoamine oxidase (MAO) genes have been associated with PG in males, as two studies found an association with the *MAO-A* (intron 1) 4-repeat allele and one study found an association with the *MAO-A* (promoter) 3-repeat allele (de Castro, Ibáñez, Saiz-Ruiz, & Fernández-Piqueras, 2002; Ibañez, de Castro, Fernandez-Piqueras, Blanco, & Saiz-Ruiz, 2000).

A small number of studies have concurrently examined an array of polymorphisms. Comings et al. (2001) analyzed the 31 genes (at 31 matched loci) involved in dopamine, serotonin, norepinephrine, and γ-aminobutyric acid pathways and found that 15 dopamine, serotonin, and norepinephrine genes contributed approximately equally to the risk for PG, with each gene accounting for <2% of the variance, totaling in accounting for between 15 and 21% of the variance in pathological gambling. The only genome wide association study (GWAS) to date was conducted on 1,312 Australian twins, with over 2M single-nucleotide polymorphisms (SNPs), examining gene associations to symptoms of PG (Lind et al., 2012). Although no SNP reached genome-wide significance ($p < 7.2 \times 10^{-8}$), six achieved p-values $< 1 \times 10^{-5}$, with variants in three genes (*MT1X, ATXN1*, and *VLDLR*) which are thought to be associated with other psychopathological disorders (e.g., alcohol and opiod dependence, schizophrenia, bipolar and unipolar depression). These findings corroborate the common difficulty faced in identifying genome-wide significant variants of large effect for addictive disorders (Treutlein & Rietschel, 2011).

An Endophenotype Approach to Pathological Gambling

Despite robust evidence of a substantial amount of genetic influence on the etiology of PG, there has been difficulty in identifying specific candidate genes that consistently account for large variation in the disorder. Given the difficulty of accounting for a large portion of the variance in PG with specific genotypes and the common associations of specific variants to multiple addictive disorders and mood disorders (Lobo & Kennedy, 2009), an endophenotype approach has been proposed to clarify genetic contributions to PG liability by elucidating the underlying mechanisms of these influences. The endophenotype approach seeks to examine simpler, more narrow phenotypes that are putatively more closely tied to a specific genetic basis within a limited number of genes.

One phenotype that has been linked to SUDs as well as PG is impulsivity. A number of well-validated self-report questionnaires of impulsivity have been associated with PG when compared to non-gambling controls such as the Barratt Impulsivity Scale (BIS; Carlton & Manowitz, 1994; Fuentes, Tavares, Artes, & Gorenstein, 2006; Petry, 2001a; Rodriguez-Jimenez et al., 2006), the Eysenck Impulsivity Questionnaire (Blaszczynski, Steel, & McConaghy, 1997), the California Personality Inventory Ego Control Scale (McCormick & Taber, 1987), and the Zuckerman Sensation Seeking Scale (Potenza et al., 2003). For example, impulsivity scores on the Eysenck Impulsivity questionnaire have been associated with symptom severity in treatment seeking gamblers (Blaszczynski et al., 1997), and with disordered gambling in undergraduates and adolescents (MacKillop, Anderson, Castelda, Mattson, & Donovick, 2006a; Nower, Derevensky, & Gupta, 2004). However, self-report measures have notable shortcomings, such as susceptibility to demand characteristics and social desirability differences between addicted participants and controls. Additionally, impulsive subjects may answer self-report questionnaires

more erratically and with less consideration than their non-impulsive peers. Finally, self-report assumes that individuals have the adequate insight to rate their personality accurately (Verdejo-García, Lawrence, & Clark, 2008).

An alternative index of impulsivity is delayed reward discounting (DRD), which measures a person's preferences for small rewards available immediately over larger rewards in the future (Bickel and Marsch, 2001). Notably, PG groups have been shown to have greater discounting of larger future rewards in favor of smaller immediate rewards (MacKillop, Anderson, Castelda, Mattson, & Donovick, 2006b; Petry & Casarella, 1999; Petry, 2001b) and greater discounting has been associated with severity of gambling behavior (Alessi & Petry, 2003). These associations have been verified in a meta-analysis which found consistent strong associations (Cohen's d = .79) between clinical levels of PG and future discounting (MacKillop et al., 2011). Additionally, numerous studies have identified DRD as temporally stable in adolescents and adults up to multiple years (Anokhin, Golosheykin, Grant, & Heath, 2011; Audrain-McGovern et al., 2009).

Delayed Reward Discounting as an Endophenotype

Delay reward discounting has been studied as a model for self-control across numerous general and clinical samples and offers a promising endophenotype for PG and other addictive disorders (Mackillop, 2013). As a behavioral characteristic, it largely satisfies the five criteria used as a standard for endophenotypes: 1) the endophenotype is associated with illness in the population; 2) the endophenotype is heritable; 3) the endophenotype is primarily state-independent (manifests whether or not the illness is active); 4) within families, endophenotype and illness co-segregate; 5) the endophenotype found in affected family members is found in

nonaffected family members at a higher rate than in the general population (Gottesman & Gould, 2003).

The aforementioned findings support that DRD is consistently associated with PG and is generally stable over time in adults. Furthermore, the heritability of DRD has been supported by evidence from studies with both animals and human twins. Studies of 344 Lewis and Fischer inbred rodents reared in identical environments have identified systematic differences in discounting across strains that are attributable to genetic differences (Anderson & Woolverton, 2005; Madden, Smith, Brewer, Pinkston, & Johnson, 2008; Stein, Pinkston, Brewer, Francisco, & Madden, 2012). Using six strains, one group found significantly greater discounting in Fischer rats compared to Copenhagen and Noble rats, but failed to replicate differences between Lewis rats (Wilhelm & Mitchell, 2009). However, a recent study suggested that this replication failure may be due to the method of task administration rather than the strain (Stein et al., 2012). Additionally, heritability evidence has been demonstrated in studies of mice that found between-strain differences (Isles, Humby, Walters, & Wilkinson, 2004). In the only study of the heritability of DRD in humans to date, Anokhin et al. (2011) assessed early adolescent twins using a single item discounting measure and found evidence of additive genetic influences at both age 12 and 14. Additionally, they found that genetic and nonshared environmental factors at age 12 predicted discounting at age 12 and 14. This finding suggests that discounting is heritable and additively influenced by environmental factors.

Studies examining the level of future discounting in individuals who do not have the disorder, but have a family history (FH) have been mixed. One study found more impulsive discounting in FH+ (paternal alcohol dependence) women, but not men (Petry, Kirby, & Kranzler, 2002), while another found no differences (Crean, Richards, & de Wit, 2002). Finally,

another found greater discounting in FH+ adolescents at a statistical trend level (Herting, Schwartz, Mitchell, & Nagel, 2010). These findings may be limited in part, because of small sample size and the explicit focus on FH of alcohol dependence without explicitly controlling for the presence of other forms of addictive behaviors in both the control and comparison conditions. Most recently, a study of 298 individuals carefully characterized the FH status of alcohol and other drug use and found FH+ status of alcohol and other drug use disorders was associated with more impulsive discounting (Acheson, Vincent, Sorocco, & Lovallo, 2011). This large and highly systematic study demonstrates strong support for an association between FH+ status of alcohol or other SUDs and discounting.

Preliminary work has been conducted examining candidate genes that confer risk for impulsive discounting. One study found an association between possession of at least one *DRD2/ANKK1*-TaqIA SNP A1 (T) allele (rs1800497) and greater discounting, as well as an interaction with the long form of the dopamine D_4 receptor gene (*DRD4* VNTR) to exhibit higher levels of impulsive discounting (Eisenberg et al., 2007). An additional study found that nonclinical young adults who were C allele carriers of the *DRD2* C957T SNP (rs6277) demonstrated more rapid responding during discounting, but not more impulsive discounting (White, Lawford, Morris, & Young, 2009).

Three studies have identified evidence for an association between the *COMT* val158met SNP (rs4680) locus related to the dopamine D_2 gene and discounting. The first study examined recovered alcoholics and healthy controls and found that those homozygous for the val variant, exhibited significantly higher discounting (Boettiger et al., 2007). The second study examined this relationship in boys with ADHD and healthy controls and found that those that were homozygous for the met variant demonstrated significantly higher discounting (Paloyelis,

Asherson, Mehta, Faraone, & Kuntsi, 2010). To reconcile these contradictory findings in a third study, Smith and Boettiger (2012) examined age effects, finding that among met-carriers, discounting was negatively correlated with age from late adolescence to adulthood, while among val/val individuals, discounting was positively correlated with age. This study further accounted for the past discrepancy by finding that val/val adults had enhanced DRD, and met/met adolescents had enhanced DRD. The authors suggest this is attributable to differences in frontal dopamine receptor concentrations between age groups, and that a deficit or an excess (in adolescence and adulthood, respectively) is thought to impair executive functioning (Arnsten, 1997; Goldman-Rakic, 2000; Williams & Castner, 2006; Zahrt, Taylor, Mathew, & Arnsten, 1997).

Of note, among the limited number of molecular genetic studies conducted to date, there is suggestive evidence that the aforementioned polymorphisms associated with greater discounting are also associated with hypofunction of the DA system. For example, the val allele of *COMT* is associated with more enzymatic rapid degradation of dopamine (Savitz, Solms, & Ramesar, 2006) and, for the *DRD2* C/T polymorphism (rs6277), the C allele is associated with reduced D_2 binding (Hirvonen et al., 2004). Further support for this hypothesis comes from fMRI and animal model studies finding the ventral striatum to be implicated in discounting. The ventral striatum is a primary region in the cortico-mesolimbic dopamine system and a recent fMRI meta-analysis of activity during discounting revealed consistent activation in the ventral striatum (Carter, Meyer, & Huettel, 2010). Lesioning the ventral striatum in an animal model of discounting has been shown to induce significantly more impulsive delay and probability discounting (Cardinal & Howes, 2005; Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001). Additionally, in line with aforementioned behavioral differences in discounting, Lewis

rats possess fewer dopamine D_2 and D_3 receptors and transporters in the striatum compared to Fischer rats (Flores, Wood, Barbeau, Quirion, & Srivastava, 1998). However, other studies have not identified hypofunction of the dopamine system as an underlying mechanism of impulsive discounting (Koffarnus, Newman, Grundt, Rice, & Woods, 2011; Pine, Shiner, Seymour, & Dolan, 2010). It is also noteworthy that the serotonergic system has been implicated in delay discounting (Bevilacqua et al., 2010; Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2000; Mobini, Chiang, Al-Ruwaitea, et al., 2000) as well as interactions between the serotonergic and DA systems (Winstanley, Dalley, Theobald, & Robbins, 2003; Winstanley, Theobald, Dalley, & Robbins, 2005).

Current Study

The goal of the current study was to examine DRD as an endophenotype for PG. More specifically, the study sought to extend the understanding of the genetics of PG by examining genetic associations with DRD and, where present, investigate whether they link those loci with PG severity. Three different strategies were employed to pursue this. First, the study used an *a priori* approach to examine previous loci that have been associated with DRD. The first hypothesis was that the *DRD2*/*ANKK1*-TaqIA SNP A1 (T) allele (rs1800497) would be associated with DRD and this effect would be moderated by possession of the long form of the *DRD4* VNTR gene (Eisenberg et al., 2007). Second, we hypothesized that the *COMT* SNP rs4680 would be associated with DRD, although we did not make a specific allelic prediction based on the conflicting findings (Boettiger et al., 2007; Paloyelis et al., 2010; Smith & Boettiger, 2012). The second strategy was to expand the examination of the *a priori* loci to other loci in relative genomic proximity. In particular, because the TaqIA polymorphism is actually located in the *ANKK1* gene and other studies suggest its association with addiction phenotypes

may be attributable to linkage to other nearby loci (Dick et al., 2007; Gelernter et al., 2006), we examined nearby polymorphisms in *DRD2*, *ANKK1*, *TTC1*, and *NCAM1*. In addition, the *COMT* candidates were expanded to relatively nearby loci based on the complex patterns of linkage disequilibrium in that gene (Mukherjee et al., 2010). In addition to individual locus associations, based on evidence that specific haplotypes (i.e. combinations of nearby loci that tend to be inherited together) in these regions may actually be more informative than the individual SNPs (Gelernter et al., 2006; Nackley et al., 2006), the third strategy was an exploratory analysis of associations of a broader panel of SNPs implicated in the DA system with DRD. Concurrently examining diverse sources of genetic variation within a candidate neurotransmitter system has been profitably used to investigate the genetic basis for sensation seeking (Derringer et al., 2010) and we applied a similar approach in relation to DRD. These strategies were then complemented with two integrative statistical approaches. Using the significantly associated loci from these strategies, we examined whether a mechanistic relationship was attributable among the genetic variables, DRD, and PG severity. Specifically, we sought to determine whether DRD is the mechanism by which a locus is associated with PG. This was accomplished using formal mediation analysis, testing for the significance of an indirect effect of DRD on the relationship between the implicated loci and PG (Figure 1). Finally, we integrated the individual significant associations using an aggregate genetic risk score (AGRS; McGeary et al., 2012) and similarly examined the interrelationships among the AGRS, DRD, and PG.

CHAPTER 2

METHOD

Sample

This study used data from a parent study (Goodie et al., 2009-2012). The study sample comprised 349 frequent gamblers (i.e., gambled at least weekly), who were recruited via newspaper advertisements and word of mouth.

Procedure

Participants were screened over the phone (exclusionary criteria: not gambling at least once a week, currently living with someone who already completed the study, computer illiteracy, psychotic symptoms, or younger than 18 or older than 65 years of age). After completing the informed consent, participants completed a diagnostic interview for PG, a variety of self-report questionnaires, including a DRD task, and submitted a DNA sample. Following participation, participants rolled a six-sided die to determine if they would receive one randomly selected outcome from their choices on the DRD task (Kirby, Petry, & Bickel, 1999), provided in cash either immediately or after the delay. Additionally, participants were compensated $30 for their participation. All procedures were approved by the University of Georgia Institutional Review Board.

Measures

Demographics. Comprehensive demographics were assessed including, sex, age, race, gender, income, education and other descriptive variables.

Pathological gambling. The Structured Clinical Interview for Pathological Gambling (SCI-PG) (Grant, Steinberg, Kim, Rounsaville, & Potenza, 2004) is a semi-structured interview that was used to assess participants' current and heaviest gambling periods. The SCI-PG is based on the 10 DSM-IV symptoms of pathological gambling.

Delayed reward discounting. Participants were administered the Monetary-Choice Questionnaire (MCQ) (Kirby et al., 1999), which consists of 27 randomized choices between smaller immediate rewards and larger delayed rewards. For example, participants were asked on the first trial, "Would you prefer $54 today, or $55 in 117 days?" They were to then place a check by which of the two reward options they would prefer. The rewards ranged from $7 to $80, and the larger delayed rewards were available at varying intervals of delay from 1 week to 186 days.

Genotyping. For DNA analysis, a saliva sample was obtained from each participant using Oragene DNA collection kits. Sufficient DNA for the candidate polymorphisms was extracted from 100% of the saliva samples. Genotyping of 384 SNPs (236 dopamine-related loci, including the *a priori* loci; the remaining unrelated to this project) was conducted using the Illumina BeadXpress and DRD4 VNTR genotyping was conducted using polymerase chain reaction (PCR). These loci were identified based on previous association studies, meta-analyses, and recent high-dimensional genotyping studies using systematic genomic interrogation (Bergen et al., 2009; Berrettini & Lerman, 2005; Dick et al., 2007; Gelernter et al., 2006; Ho & Tyndale, 2007; Hodgkinson et al., 2008; Kreek, Nielsen, Butelman, & LaForge, 2005; Munafò, Clark, Johnstone, Murphy, & Walton, 2004; Nackley et al., 2006; Yu et al., 2006; Zhang et al., 2006).

Data Analysis

Delayed reward discounting. An estimate of a participant's impulsivity (i.e., k) can be made from the participant's pattern of choices across the 27 MCQ questions (Kirby et al., 1999). The k value in this case reflects the hyperbolic discounting function that exhibits the highest consistency among the participants' choices. For example, a person with a discount rate of 0.10 would be indifferent between "$33 today" and "$80 in 14 days," so if they chose the smaller immediate reward, then they would have a discounting rate greater than 0.10. In a question where the immediate reward is less and the delayed reward is larger and sooner (e.g., "$31 today" or "$85 in 7 days"), a discounting rate of 0.25 would demonstrate indifference between those two rewards. If the participant chose the delayed reward here, then they would have a discounting rate less than 0.25. From these two trials, it could be inferred that the participant has a discount rate between 0.10 and 0.25. The geometric mean of all 27 items is used to calculate the k values to avoid underweighting the smaller parameter (e.g., in this example $k = 0.16$). The discount rate that yields the highest consistency across trials was be utilized to estimate each participant's k value, and in the instance where two or more k values are equally consistent, their geometric mean was computed. As a validity check, a magnitude effect (i.e., greater discounting for smaller rewards than larger rewards) was examined using a within-subjects analysis of variance (ANOVA). To examine this effect, the delayed rewards used in the questionnaire were grouped into three reward sizes: small ($25 to $35), medium ($50 to $60), and large ($75 to $85). In this way, a separate k value was calculated for small, medium, and large delayed rewards.

Candidate gene associations. PLINK software was used to examine genotype-phenotype associations (Purcell et al., 2007). To maximize resolution in both *a priori* and exploratory

analyses, the number of minor alleles (i.e., 0, 1, or 2) was examined in relation to the phenotype using an additive model. Based on prior research (see Table 2), DRD4 VNTR was dichotomized into 7 allele versus < 7 allele carriers. Regression analyses for testing SNP, dichotomized VNTR, and haplotype associations with DRD were conducted using empirical significance values.

Moderation. DRD4 VNTR and rs1800497 were centered about the mean prior to conducting moderation analysis. Then *DRD4* VNTR and rs1800497 were entered into the first step of a hierarchical linear regression model, followed by the interaction effects of *DRD4* VNTR and rs1800497.

Haplotype Analysis. Haplotype blocks were identified using Haploview (Barrett, Fry, Maller, & Daly, 2005) and LD was defined as 95% confidence of non-random association of alleles at two or more loci (Gabriel et al., 2002). Haplotype blocks containing SNPs from chromosome 11 and 22 that were found to be significantly associated with DRD were analyzed for haplotype associations to DRD. Individual and haplotype associations were then concurrently examined to determine the most appropriate interpretation.

Aggregate genetic risk score. Following identification of statistically significant SNPs from chromosome 11 and 22 and from the exploratory panel, we examined all significant SNPs summed into an AGRS, in relation to DRD. Aggregate genetic risk scores were calculated using the following formula:

AGRS = (sum of risk allele scores/number of non-missing genotypes × 2) × (2 x total number of SNPs in the AGRS) (Cornelis et al., 2009). This simple count method of calculating the AGRS assumes an additive genetic model where equivalent effects of each polymorphism and pathological gambling are expected. This model does not allow for epistatic effects. For each

significant SNP, participants were given a score (i.e., 0, 1, or 2) denoting the number of risk alleles they possess.

Mechanistic analyses. To test whether DRD reflects an indirect relationship between genetic variation and PG severity, we conducted analyses of mediational relationships for all SNPs significantly associated to DRD. Mediation and partial mediation was determined using 95% confidence intervals of the Sobel specialized t-test, which determines whether the relationship between the independent variable (genotype) and dependent variable (PG severity) is significantly reduced after DRD is included as the mediator in the model (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). In the absence of a significant association between the independent variable and dependent variable, the significance of the indirect effect was still tested because the direct relationship may not be present due to low power or suppression effects (Mackinnon & Fairchild, 2009).

CHAPTER 3

RESULTS

Preliminary Analyses

The initial sample consisted of 349 genotyped participants. Five participants were excluded for missing >15% genotypes. However, several lines of evidence supported conducting analyses on EAs only ($N = 175$) within this study. First, there were significant demographic and phenotypic differences between EAs and African Americans (AAs; $N = 143$) across all observed variables except for age (sample characteristics summarized in Table 5). Notably, despite demonstrating a similar propensity to discount small rewards at a greater rate than medium rewards, and medium rewards at a greater rate than large rewards, EAs showed a reduced level of DRD overall as compared to AAs. Furthermore, there were significant differences in associations between the correlations of the primary phenotypes of interest (i.e., PG severity and DRD), summarized in Table 6. Most notably, in EAs there was a medium effect size relationship between k and PG severity ($r = .40$, $p < .01$), whereas in AAs there was no significant relationship between k and PG severity ($r = .12$, $p = .16$), and this correlation was significantly less than the correlation in EA's ($p < .01$). Finally, allelic frequencies notably differed between the two samples for a number of loci. Given these sample differences, association differences, and allelic frequency differences, the study only focused on individuals of European ancestry (i.e., European Americans; EAs). This analytic approach circumvents the confounding effects of population stratification (Hutchison, Stallings, McGeary, & Bryan, 2004).

With regard to genotyping, of an initial panel of 236 dopamine-related loci genotyped, SNPs with excessive missing data (>20%) and insufficient variability (<10%) were excluded from further consideration, leaving 153 SNPs. Hardy-Weinberg equilibrium (HWE) was included to identify abnormal genotype frequencies, however, given the recruitment characteristics of this sample (i.e. high frequency of gambling), SNPs were not excluded prior to analyses for abnormal frequencies (Sham, 1998). Detailed characteristics (including HWE) of all SNPs used in analyses are reported in Table A1 of the appendix.

***a priori* Loci**

No statistically significant associations were found between the *a priori* loci *DRD4* VNTR (7R), *ANKK1/DRD2* (rs1800497), *COMT* (rs4680) and *k* (see Table 7). Analyses were conducted examining if there was a moderating effect of possession of the long form (7R) of *DRD4* VNTR on the association between possession of the minor allele (T) of rs1800497 and *k*. When including both genes in the first step of a linear regression model and the interaction effects in the second step, no significant moderating effects were found ($r = .06$, $p = .45$).

Chromosome 11 and 22 and Haplotype Analyses

Analyses for 65 SNPs from chromosome 11 and 12 SNPs from chromosome 22 were conducted. Of these, four SNPs from chromosome 11 (rs2288158, rs2303380, rs4938013, rs2440390), and one from chromosome 22 (rs6269) were significantly associated with *k* at $p < .05$. Possession of the minor allele for rs2288158 from gene *NCAM1* was associated with less impulsive discounting. Possession of the minor allele in the other four significant SNPs from genes *TTC12*, *ANKK1*, *DRD2*, and *COMT*, respectively, was associated with more impulsive discounting.

Notably, none of the four individual SNPs were significantly associated with PG directly, so the Sobel t-tests conducted were examining a pathway relationship to determine if DRD is the pathway through which these SNPs incrementally contribute to variance in PG severity. Analyses verified a relationship between three SNPs (rs2288158, rs2440390, rs6269) and PG severity, mediated by DRD at $p < .05$. The other two SNPs remained at a trend level of significance ($p < .10$). Detailed results of individual and mediational relationships can be found in Table 7.

Linkage disequilibrium analysis identified nine haplotype blocks on chromosome 11 and two haplotype blocks on chromosome 22. Haplotype association analysis was conducted on four blocks containing the significantly associated SNPs with the exception of rs2440390, which was not in LD. Haplotype analyses suggested that no individual SNP relationships were better accounted for by haplotypes. Notably, however, LD block rs165656/rs6269/rs2239393/rs4680, contains the *a priori* SNP from the *COMT* gene (i.e., rs4680). Detailed haplotype analysis results are summarized in Table 8 and characterization of LD blocks for EAs is depicted in Figure 2.

Exploratory Dopaminergic Panel

Exploratory analyses for 76 additional SNPs within the DA system were conducted. Of these, six SNPs (rs13106539, rs686, rs10499696, rs363332, rs363334, rs363338) were significantly associated with *k.* In order, the first three SNPs are within genes *DRD5*, *DRD1*, and *DDC*, and the latter three SNPs are within the gene *SLC18A2*. Interestingly, possession of the minor allele in the latter five SNPs served as a protective factor (i.e., less discounting), whereas possession of the rs13106539 *DRD5* minor allele was associated with greater discounting. None of the 6 individual SNPs were significantly associated with PG directly, so the Sobel t-tests were again conducted on indirect associations between the SNPs and PG severity through DRD.

Analyses verified a relationship between three SNPs (rs363332, rs363334, rs363338) and PG severity, mediated by DRD at $p < .05$. The other three SNPs remained at a trend level of significance ($p < .10$). Detailed results can be found in Table 7.

Aggregate Genetic Risk Score

An AGRS including all 11 significant SNPs (maximum possible AGRS = 22) was calculated. Results yielded a significant association between this AGRS and k ($r = .34$, $p < .001$). Interestingly, the AGRS comprised of 11 significant SNPs was significantly associated with PG ($r = .15$, $p < .05$) and this relationship was significantly mediated by k ($t = 3.63$, $p < .001$). In a model including k, the relationship between AGRS and PG was reduced to non-significance ($r = .02$, $p = .83$), suggesting full mediation by k.

CHAPTER 4

DISCUSSION

This study sought to examine the role of DRD as an endophenotype for PG. A biological systems approach was utilized for this study, whereby loci from the genes directly associated with the DA system were included to examine this relationship (see Table 4). Specifically, *a priori* candidate genes (*DRD4* VNTR, *ANKK1/DRD2* (rs1800497), *COMT* (rs4680)), proximal genes on chromosome 11 and 22, and a broader exploratory panel of DA genes were examined for significant relationships with DRD.

For the first strategy, previous associations between *DRD4* VNTR, rs1800497, and rs4680 and DRD were not found within this study. The current findings were inconsistent with the previous study that identified an association between rs1800497 and greater discounting, and moderation of that finding by the long form of *DRD4* VNTR (Eisenberg et al., 2007). However, numerous differences were present in this study which could explain the absence of an association (e.g., lower SES, community recruited, gambling at least once per week, 100% EA, DRD task differences). Given the associations of rs4680 with discounting in three previous studies (Boettiger et al., 2007; Paloyelis et al., 2010; Smith & Boettiger, 2012), the absence of a relationship here was somewhat more surprising. However, existing findings are somewhat inconsistent, with the first study finding val/val as the risk genotype, the second finding met/met as the risk, and then the third study finding age effects. Furthermore, rs4680 was found to be in LD with a significantly associated SNP, rs6269, which holds implications for its role in impulsive decision making (discussed in detail below).

Despite null findings in the *a priori* SNPs, this study identified several potential candidate markers significantly accounting for variance in DRD. Four SNPs from chromosome 11 (*NCAM1* (rs2288158), *TTC12* (rs2303380), *ANKK1* (rs4938013), *DRD2* (rs2440390)) and one from chromosome 22 (*COMT* (rs6269)) were identified as being significantly associated. Notably, no individual relationships were better accounted for by haplotype blocks. However, haplotype analyses identified rs6269 to be in linkage with rs4680 (rs165656/rs6269/rs2239393/rs4680). This is consistent with previous research which found rs6269 to be in a LD block with rs4680 (rs6269/rs4633/rs4818/rs4680) and to be the only SNP significantly associated with reduced executive functioning in ADHD children. This suggests that rs6269 may be the true source of variance (instead of rs4680) within the *COMT* gene in executive functioning deficits contributing to impulsive decision making.

The specific functionality of the SNPs rs2288158, rs2303380, rs4938013, and rs2440390 have not been studied in detail, however, *NCAM1*, *TTC12*, and *ANKK1* may be related to dopamine receptor D_2 functionality or other aspects of brain function (Mota, Aruajo-Jnr, Paixao-Cortes, Bortolini, & Bau, 2012; Neville et al., 2004). Despite an absence of research on functionality, the A allele of rs2303380 has been associated with lower PG severity (Lobo et al., 2010) and the G variant has been associated with higher nicotine dependence (Gelernter et al., 2006) and smoking initiation (as part of a larger haplotype) (David et al., 2010). These findings parallel this current study which identified the G variant to be associated with higher DRD. Furthermore, rs4938013 has been previously associated with heroin dependence (Nelson et al., 2013) as well as nicotine dependence (Gelernter et al., 2006). This is the first study, to the authors' knowledge, to identify rs2288158 and rs2440390 as contributing to addictive disorders.

Finally, examination of the broader DA system yielded six SNPs significantly associated with DRD (*DRD5* (rs13106539), *DRD1* (rs686), *DDC* (rs10499696), *SLC18A2* (rs363332, rs363334, rs363338)). The specific functionality of the SNPs rs13106539, rs10499696, rs363332, rs363334, and rs363338 have not been studied in detail, however, the role of *DRD5*, *DDC*, and *SLC18A2* in the DA system is summarized in Table 4. The D_1 receptor is thought to mediate long-term neuroadaptation in the reward circuit and, similarly, the consolidation of addictive behaviors (Bahi & Dreyer, 2012; Dudman et al., 2004).The *DRD1* SNP rs686 minor allele is thought to decrease *DRD1* receptor activity, which, in turn, decreases overall excitatory DA activity (Huang & Li, 2009). The protective effect of the rs686 minor allele has been found to be present in an association with longer transition to dependence in Chinese opiod users (Zhu et al., 2013), with lower nicotine dependence in EA and AA smokers (Huang et al., 2008), and with lower alcohol dependence and fewer withdrawal seizures (Batel et al., 2008). Interestingly, the same minor allele was associated with less DRD in this study. These findings provide evidence that the rs686 minor allele may serve as a protective factor by decreasing D1 receptor activity. This is inconsistent with the hypothesis of an inverse relationship between DA neurotransmission and impulsive DRD (i.e., ↓ DA, ↑ DRD), however, other studies have also not implicated dopaminergic hypofunction in impulsive discounting (Koffarnus et al., 2011; Paloyelis et al., 2010; Pine et al., 2010). Thus, it may be that this hypothesis is either incorrect or oversimplifies the relationship. Disentangling the underlying neurobiology is clearly a high priority as this line of research progresses.

An AGRS was summed for analyses in this study, including all 11 significantly associated SNPs. It was significantly associated with DRD above the effect sizes attributable to any individual SNPs. Furthermore, it was significantly associated with PG. This finding is

consistent with a biological systems approach, whereby possession of a single risk variant may not translate directly to the disorder, however, possession of numerous risks can precipitate an increased relationship with the endophenotype as well as a direct relationship with the disorder (McGeary et al., 2012). This suggests that small individual associations may additively be associated with mechanistic and clinical phenotypes.

Mechanistic analyses identified DRD as an intermediate variable between six of the individual SNPs (rs363332, rs363334, rs363338, rs2288158, rs2440390, rs6269) and PG. This suggests DRD is a pathway for these specific candidate markers and PG severity in EAs. The indirect effects for the remaining five SNPs were present at the level of statistical trends, suggesting a parallel relationship. Most importantly, however, was the finding that the direct relationship between the 11 SNP AGRS and PG was fully mediated by DRD. This finding provides preliminary evidence that individuals with multiple DA risk alleles for DRD have more PG symptoms and this relationship is accounted for by the relationship by these DA SNPs and DRD. Furthermore, this finding renders it unlikely that AGRS is having a pleiotropic effect on PG because DRD is a full mediator of the relationship, suggesting there is no independent association between the AGRS and PG.

In spite of the promising findings presented here, this study had at least three notable limitations. First, this study was exploratory in nature, meaning the identified associations ($p < .05$) would not survive stringent type I error correction (e.g., Bonferroni) and therefore future replication will be necessary to establish these relationships. Second, this study only considered the DA system, which accounted for approximately 12% of the variance in DRD. Although, this is a notable proportion of genetic variance in DRD, this suggests additional candidate neurotransmitter systems need exploration to account for all genetic variation in this index of

impulsivity. Third, AAs (and all other non-EA races) were excluded from analyses in this study. This decision was based on numerous factors, the first being that AAs were substantively different in demographic characteristics, PG severity, and level of discounting. Most importantly, however, AAs had no association between DRD and PG while EAs had a medium effect size relationship between the two variables of interest. Finally, due to the confounding effects of population stratification it would have been suboptimal to pool all races into one population for genetic analyses. These meaningful differences between EAs and AAs suggest that there may be a different phenotypic relationship between DRD and PG, although racial differences in discounting have received limited study to date.

Despite its limitations, this study represents an important step forward in understanding the genetic basis of PG as well as the intermediate risk phenotype, DRD. This is the first study to systematically study genetic associations to DRD. Specifically, this study examined the broader DA system and expanded the boundaries of possible genes in accounting for variation in impulsive decision making and PG. Results suggest that certain DA loci play a significant role in the propensity to devalue large delayed rewards in favor of small immediate rewards (i.e., DRD), and that this propensity is a possible endophenotype for PG in EAs. Given the absence of an association between DRD and PG in AAs, and the remaining variance unaccounted for in PG in EAs, there are many promising avenues for future research that explore additional possible endophenotypes for this disorder. The findings here provide provocative new evidence of DRD as a promising endophenotype for PG, particularly when considering genes in aggregation. These promising and novel findings here await future replication and extension.

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Table 1

Genetic contributions to gambling behavior and pathological gambling (PG) symptoms

Authors	*Sample*	*Gambling symptomatology assessed*	*Results*
Blanco et al. (2012)	Web Based Sample (1737; 1739; 67% female)	Gambling Frequency (GF); Lifetime PG symptoms (categorized)	Additive genetic influence on GF = 32%; PG = 83%
Slutske et al. (2011); Slutske et al. (2010)	Australian Twin Registry (4,764; 57% female)	Lifetime PG symptoms (SOGS+ DSM-IV from Slutske et al. (2010))	Additive genetic influence average between the two measures of 52%
Beaver et al. (2010)	National Longitudinal Study of Adolescent Health (602; 51% female)	Measure designed to assess gambling problems	Additive genetic influence of 72%
Slutske et al. (2009)	Australian Twin Registry (4,764; 57% female)	Lifetime involvement in any form of gambling	Additive genetic influence of 55%.
Xian et al. (2007)	Vietnam Era Twin Registry (1,675 males)	Lifetime and current PG symptoms	No difference in genetic contributions to lifetime and past year gambling symptoms 10 years later despite unique environmental influences.
Slutske et al. (2000)	Vietnam Era Twin Registry (3,372 males)	PG diagnosis	Risk for PG significantly higher among MZ (6.1%) and DZ (3.1%) co-twins of men with subclinical PG symptoms than co-twins of men with no PG symptoms

Eisen et al. (1998)	Vietnam Era Twin Registry (6,718 males)	PG diagnosis	Additive genetic influence of 62%
Winters and Rich (1998)	Minnesota Twin Study (155; 41% female)	“High-action” and “low-action” gambling	Males MZ significantly more similarity on gambling frequency of “high-action” games. No differences by twin type on gambling frequency of “low-action” games

Note. MZ = monozygotic twins; DZ = dizygotic twins.

Table 2

Molecular genetic association studies in pathological gambling (PG)

Authors	*Sample*		*Polymorphisms*	*Results*
	Cases	Controls		
Comings et al. (1996)	222 PG	714	DRD2 TaqIA	Association with allele T
Perez de Castro et al. (1997)	68 PG	68[1]	DRD4 (exon III)	7-repeat allele associated with PG in females
Comings et al. (1997)	163[a] PG	124[a]	DRD1 Ddel	Association with allele A1
	186[a] PG	138[a]	DRD2 TaqIA	Association with allele T
Perez de Castro et al. (1999)	68[b] PG	68[b]	5HHT-LPR	Short allele associated with PG in males
Comings et al. (1999)	165[a] PG	124[a]	DRD4 (exon III)	5-8-repeat and 7-repeat alleles associated with PG
Ibanez et al. (1999)	68[b] PG	68[b]	TH (intron 1)	
Ibanez et al. (2000)	68[b] PG	68[b]	MAO-A (intron 1) MAO-A (promoter) MAO-B (intron II)	4-repeat allele associated with PG in males 3-repeat allele associated with PG in males
Comings et al. (2001)	139 PG	139[1]	31 genes involved in dopamine, serotonin, noradrenaline and GABA neurotransmitters	Genes in dopaminergic, noradrenergic and glutamatergic neurotransmitter systems accounted for <2% of the variance in PG
Perez de Castro et al. (2002)	68[b] PG	68[b]	MAO-A (promoter)	3-repeat allele associated with more severe forms of PG in males
da Silva Lobo et al. (2007)	140 PG	140[2]	DRD1 (-800T/C), DRD2 TaqIA DRD3 (Ser9 Gly) DRD4 (exon III) DRD5 (CA repeat)	Association with DRD1 allele T
Lim et al. (2012)	104 PG Korean males	114[3]	DRD1 Ddel DRD2 TaqIA DRD3 (Ser9 Gly)	No significant associations

			DRD4 (exon III)	
Lind et al. (2012)	1312 quantitative DG		2,381,914 SNPs	No associations achieved corrected significance threshold
Wilson et al. (2013)	140 [c] PG siblings	140[c]	5HHT-LPR	
			5HT-1B	
			5HT-2A	C/C genotype associated with PG

Note. [1]Ethnically-, gender- and age-matched. [2]Non-PG full siblings. [3] Age- and race-matched men. [a]Derived from the same sample as Comings et al. (1996). [b]Same sample as Perez de Castro et al. (1997). [c]Same sample as da Silva Lobo et al. (2007). GABA = gamma aminobutyric acid; *5HTT* = serotonin transporter gene; CA repeat = cystosine-adenine repeat; *DRD* = dopamine receptor gene; TH = tyrosine hydroxylase; *MAO-A* = monoamine oxidase A; *MAO-B* = monoamine oxidase B; DG = disordered gambling. Table updated from Lobo and Kennedy (2009).

Table 3

a priori candidate polymorphisms

Gene	*Locus (rs#, where applicable)*	*Putative Pathway Relevance*
DRD4 VNTR	Exon 3 variable number of tandem repeats polymorphism	7+ = ↓ D_4 receptor sensitivity
ANKK1/DRD2 C/T SNP	ANKK1 – position 17316 (rs#1800497; "TaqIA")	T = ↓ D_2 receptor density
COMT A/G SNP	COMT – position 27009 (rs#4680; val158met)	val = ↑ DA enzymatic degradation (↓ DA)

Note. DA = Dopamine; SNP = Single-nucleotide polymorphism.

Table 4

Dopamine neurotransmission pathway-based loci for exploratory analyses

Gene	*Name*	*#SNPs*	*Pathway Relevance*
DRD1	Dopamine D_1 receptor	2	D_1 receptor
DRD2	Dopamine D_2 receptor	31	D_2 receptor
DRD3	Dopamine D_3 receptor	10	D_3 receptor
DRD4	Dopamine D_4 receptor	2	D_4 receptor
DRD5	Dopamine D_5 receptor	4	D_5 receptor
SLC6A3	Solute carrier family 6 member 3 (DA transporter)	9	Reuptake
SLC18A2	Solute carrier family 18, member 2 (vesicular monoamine)	8	Reuptake
TH	Tyrosine hydroxylase	2	Synthesis
DDC	Dopa decarboxylase	15	Synthesis
DBH	Dopamine beta-hydroxylase	16	Degradation
COMT	Catechol-O-methyltransferase	12	Degradation
MAO-A	Monoamine oxidase A	8	Degradation
MAO-B	Monoamine oxidase B	4	Degradation
ANKK1	Ankyrin repeat and kinase domain containing 1	6	Linked to D_2 receptor
TTC12	Tetratricopeptide repeat domain 12	7	Linked to D_2 receptor
NCAM1	Neural cell adhesion molecule 1	17	Linked to D_2 receptor

Table 5

Participant characteristics

	EA	AA
Age	34.7 (13.1)	36.6 (11.1)
Education	13.5 (2.5)	11.7 (2.0)**
Income	2.6 (2.1)	1.5 (.82)**
PG Severity	2.8 (2.8)	4.0 (2.8)**
Small *k*	.09 (.08)[A]	.13 (.09)**[A]
Medium *k*	.08 (.08)[B]	.12 (.10)**[B]
Large *k*	.07 (.08)[C]	.11 (.10)**[C]
Average *k*	.08 (.08)	.12 (.09)**

Note. EA = European American, AA = African American, k = behavioral economic index of impulsive choice preference; significant differences between races: ** = $p < .01$; significant differences within EA and AA groups among small, medium, and large k: small-med [A] = $p < .05$; med-large [B] = $p < .05$; large-small [C] = $p < .05$.

Table 6

Associations among discounting indices and pathological gambling (PG) severity across races

	Overall				EA				AA			
Variable	1	2	3	4	1	2	3	4	1	2	3	4
1 Small *k*	---	---	---	---	---	---	---	---	---	---	---	---
2 Medium *k*	.82**	---	---	---	.83**	---	---	---	.80**	---	---	---
3 Large *k*	.79**	.88**	---	---	.77**	.90**	---	---	.78**	.85**	---	---
4 Average k	.92**	.96**	.94**	---	.92**	.96**	.94**	---	.92**	.95**	.94**	---
5 PG Severity	.31**	.27**	.26**	.30**	.40**	.36**	.36**	.40**	.13††	.11†	.11†	.12††

Note. * = $p < .05$, ** = $p < .01$; significant differences by race: † = $p < .05$, †† = $p < .01$.

Table 7

Candidate gene associations with delayed reward discounting (DRD), pathological gambling severity (PG), and mediational analyses (N = 175)

Gene Characteristics					DRD (*k*)					PG Severity					Mediation		
Chr	Gene	SNP	Mi/Ma	MAF	*β*	SE	*t*	*p*	R^2	*β*	SE	T	*p*	R^2	*t*	SE	*p*
a priori																	
11	DRD4	VNTR	7R/4R	.14	-.01	.02	-.62	.54	.002	-.07	.62	-.11	.91	.009	--	--	--
11	ANKK1	rs1800497	T/C	.20	.00	.01	.08	.93	.000	.60	.38	1.55	.12	.014	--	--	--
22	COMT	rs4680	G/A	.42	.01	.01	.65	.52	.002	-.31	.31	-1.02	.31	.006	--	--	--
Chromosome 11 and 22																	
11	NCAM1	rs2288158	C/A	.16	-.03	.01	-2.15	.03	.026	-.32	.42	-.76	.45	.003	-2.01	.18	.04
11	TTC12	rs2303380	G/A	.36	.02	.01	2.08	.04	.024	.79	.3	2.64	.01	.039	1.94	.12	.05
11	ANKK1	rs4938013[1]	A/C	.31	.02	.01	2.08	.04	.025	.28	.32	.9	.37	.005	1.96	.13	.05
11	DRD2	rs2440390[1]	A/G	.12	.03	.01	2.41	.02	.033	.38	.49	.77	.45	.003	2.21	.21	.03
22	COMT	rs6269[2]	C/T	.10	.02	.01	2.34	.02	.032	.11	.39	.29	.77	.001	2.17	.17	.03
Broader Exploratory Panel																	
4	DRD5	rs13106539	C/T	.34	.02	.01	2.00	.05	.023	-.12	.33	-.35	.73	.001	1.89	.14	.06
5	DRD1	rs686	C/T	.41	-.02	.01	-1.98	.05	.022	-.37	.3	-1.25	.21	.009	-1.87	.12	.06
7	DDC	rs10499696	C/T	.11	-.03	.01	-1.98	.05	.022	-.89	.48	-1.86	.06	.020	-1.86	.2	.06
10	SLC18A2	rs363332	A/G	.21	-.03	.01	-2.69	.01	.04	-.11	.38	-.3	.76	.001	-2.43	.17	.01
10	SLC18A2	rs363334	G/C	.22	-.03	.01	-2.74	.01	.042	-.13	.37	-.35	.73	.001	-2.47	.16	.01
10	SLC18A2	rs363338	G/A	.30	-.03	.01	-3.18	.00	.055	-.23	.33	-.71	.48	.003	-2.77	.15	.01

Note. [1] *n* = 174, [2] *n* = 165.

Table 8

Haplotype association of significant variants located on chromosome 11 and 22

Genotypes	Haplotypes	Frequency	*β*	*t*	P	R^2
Chromosome 11						
rs2303380/rs948176/rs2288159	AGA	.19	-.012	-1.12	.26	.007
	GAC	.36	.017	2.08	.04	.024
	AAC	.45	-.01	-1.11	.27	.007
rs2282511/rs877138/**rs4938012/**rs17115439/rs4938013	TCTAA	.30	.018	2.04	.04	.023
	GTCAC	.02	-.015	-.54	.59	.002
	TTCGC	.01	-.012	-.34	.73	.001
	GTCGC	.65	-.014	-1.6	.11	.014
rs1076560/rs2283265/**rs2440390**/rs2075654/rs1800498/rs2587548/ rs1076563/rs1076562/rs1079597/rs1079596/rs1125394/rs2471857/ rs7103679/rs4586205/rs4648318/rs11214608	ATGAGGTGATGATTTG	.13	.005	.37	.72	.001
	CGGGACGGGCAGCTTA	.55	-.008	-.94	.35	.005
	CGAGGGTAGCAGCGCG	.11	.03	2.16	.03	.026
	CGGGGGTAGCAGCGCG	.16	-.004	-.32	.75	.001
	CGGGGGTAGCAGCGTG	.01	-.075	-1.69	.09	.016
	CGAGGGTAGCAGCGTG	.01	.02	.46	.65	.001
Chromosome 22						
rs165656/**rs6269**/rs2239393/rs4680	GCCG	.10	.024	2.28	.02	.031
	GTCG	.21	-.015	-1.19	.24	.009
	CTCG	.01	.025	.56	.58	.002
	GTTG	.06	-.011	-.61	.54	.002
	CTTA	.60	-.007	-.76	.45	.003

Note. Bolding indicates the SNPs that were individually associated with PG.

Figure Captions

Figure 1. Schematic of mediational analytic approach. *C'* refers to the size of the relationship between the genotype(s) and PG when DRD is included as a mediator.

Figure 2. Linkage disequilibrium (LD) patterns in (Panel A) chromosome 11 and (Panel B) chromosome 22 of European Americans

Figure 1

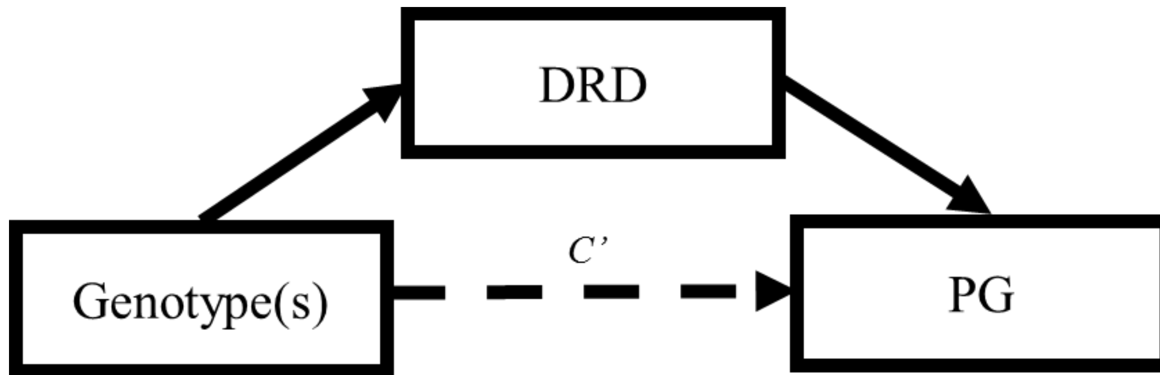
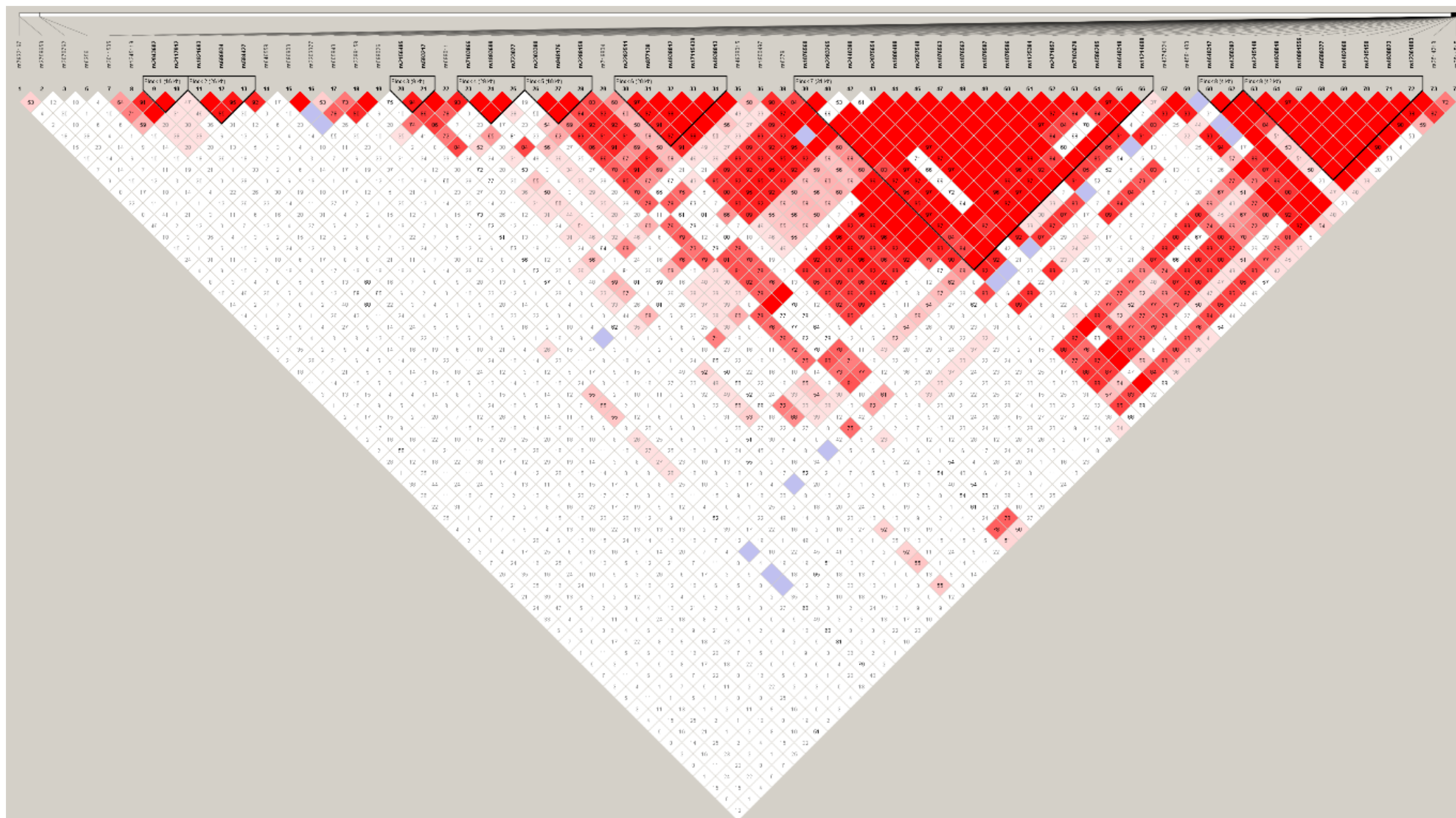
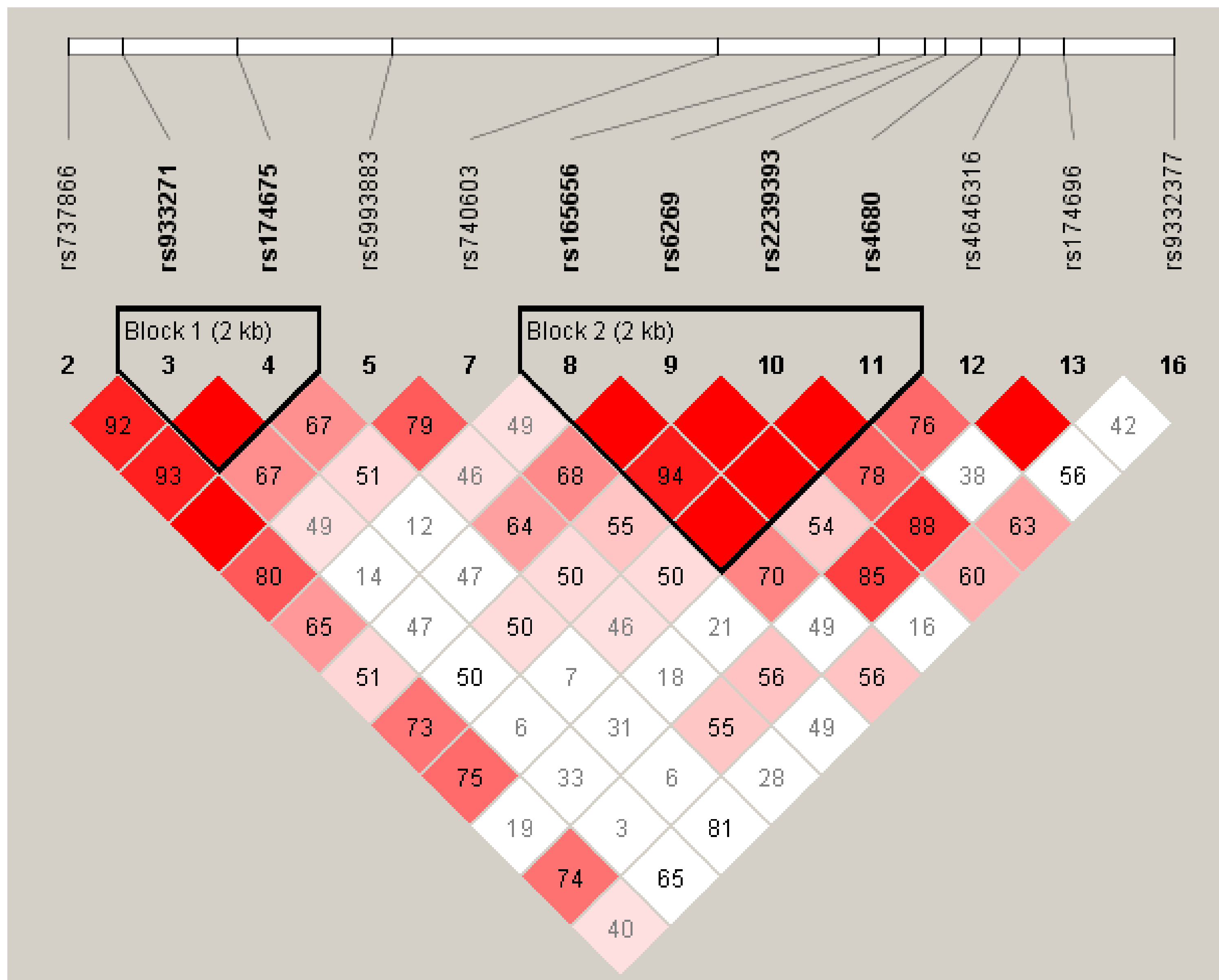


Figure 2

A



B



APPENDIX

Table A1

Single-nucleotide polymorphism (SNP) characteristics

Chr	Gene	SNP	BP Position	Participants	MAF	Min	Maj	HWE
				European Americans				
3	DRD3	rs2134655	113858201	175	.27	A	G	0.08
3	DRD3	rs963468	113862887	175	.39	A	G	1.00
3	DRD3	rs3773678	113870078	175	.17	T	C	0.01
3	DRD3	rs167770	113879562	174	.29	G	A	0.03
3	DRD3	rs324029	113881623	174	.29	T	C	0.03
3	DRD3	rs10934256	113885652	174	.2	T	G	0.64
3	DRD3	rs7633291	113887068	175	.2	C	A	0.64
3	DRD3	rs324022	113887298	175	.29	T	C	0.02
3	DRD3	rs7638876	113894300	175	.35	G	A	0.03
3	DRD3	rs9825563	113900220	174	.33	C	T	0.23
4	DRD5	rs7655090	9765875	175	.28	G	A	0.35
4	DRD5	rs10939515	9773296	175	.14	T	C	0.05
4	DRD5	rs2867383	9787935	175	.3	A	G	1.00
4	DRD5	rs13106539	9797703	175	.34	C	T	0.31
5	SLC6A3	rs6347	1411412	175	.26	G	A	0.17
5	SLC6A3	rs27048	1412645	172	.45	A	G	0.76
5	SLC6A3	rs37022	1415629	175	.19	T	A	0.01
5	SLC6A3	rs464049	1423905	175	.45	G	A	1.00
5	SLC6A3	rs403636	1438354	175	.13	T	G	0.74
5	SLC6A3	rs2652511	1446389	168	.41	A	G	0.42
5	SLC6A3	rs2652510	1447860	174	.39	C	T	0.75
5	SLC6A3	rs3756450	1448148	175	.12	G	A	0.72
5	SLC6A3	rs12652860	1453772	174	.27	A	C	1.00

5	DRD1	rs686	174868700	175	.41	C	T	0.64
5	DRD1	rs5326	174870196	175	.15	A	G	0.38
7	DDC	rs4947510	50525420	174	.28	A	G	0.26
7	DDC	rs4947535	50531681	175	.3	T	A	0.59
7	DDC	rs732215	50544063	148	.43	C	A	0.62
7	DDC	rs4490786	50544314	175	.19	A	G	1.00
7	DDC	rs2122822	50552152	175	.4	G	C	0.21
7	DDC	rs880028	50570136	175	.19	G	A	1.00
7	DDC	rs10249982	50591390	175	.22	C	T	0.82
7	DDC	rs10244632	50598703	174	.25	T	C	0.16
7	DDC	rs1466163	50607206	175	.11	A	G	1.00
7	DDC	rs7786398	50612906	175	.45	G	A	0.88
7	DDC	rs2329341	50620275	175	.31	C	A	0.73
7	DDC	rs10499696	50621588	175	.11	C	T	1.00
7	DDC	rs3829897	50629764	174	.39	A	C	0.43
7	DDC	rs7804365	50637148	175	.5	C	A	1.00
7	DDC	rs12669770	50656334	175	.34	T	C	1.00
9	DBH	rs1076153	136498143	175	.19	T	G	0.09
9	DBH	rs1076150	136498761	167	.5	C	T	0.76
9	DBH	rs1611114	136500203	171	.28	A	G	0.00
9	DBH	rs2797849	136501941	174	.35	G	C	0.62
9	DBH	rs3025388	136503256	175	.17	G	A	1.00
9	DBH	rs2007153	136503819	174	.36	A	G	0.10
9	DBH	rs2873804	136505644	172	.45	T	C	0.22
9	DBH	rs1611124	136509275	174	.1	A	C	1.04×10^{-25}
9	DBH	rs1541332	136511516	175	.46	T	C	0.45
9	DBH	rs2519154	136512275	175	.45	C	T	0.55
9	DBH	rs77905	136518097	175	.45	T	C	0.65
9	DBH	rs2073833	136520282	172	.46	G	C	0.76
9	DBH	rs1611131	136522187	175	.3	G	A	0.37
9	DBH	rs2073837	136522928	175	.31	T	C	0.05

9	DBH	rs129882	136523669	136	.18	A	G	0.57
9	DBH	rs129915	136524918	175	.29	G	A	0.28
10	SLC18A2	rs363332	119002667	175	.21	A	G	1.00
10	SLC18A2	rs363334	119004995	175	.22	G	C	1.00
10	SLC18A2	rs363338	119009389	175	.3	G	A	1.00
10	SLC18A2	rs4752045	119019690	174	.42	C	G	0.53
10	SLC18A2	rs2015586	119021737	174	.26	C	T	4.63×10^{-14}
10	SLC18A2	rs363230	119029515	175	.46	A	G	0.45
10	SLC18A2	rs2244249	119032275	152	.13	T	C	0.48
10	SLC18A2	rs363276	119033809	175	.14	A	G	0.76
11	DRD4	rs7932167	620599	174	.23	C	A	0.39
11	DRD4	rs3758653	636399	175	.17	G	A	1.00
11	TH	rs2070762	2186335	174	.5	A	G	0.88
11	TH	rs6356	2190951	175	.33	A	G	0.87
11	NCAM1	rs2011505	112988236	174	.43	C	T	0.09
11	NCAM1	rs1245119	113001661	175	.39	G	C	0.04
11	NCAM1	rs2043602	113043726	175	.39	C	T	0.63
11	NCAM1	rs2117912	113060469	173	.22	C	T	0.50
11	NCAM1	rs1821693	113077541	175	.41	C	T	0.64
11	NCAM1	rs686934	113085448	175	.41	G	A	0.64
11	NCAM1	rs584427	113103996	175	.5	T	G	0.45
11	NCAM1	rs646558	113105907	174	.22	T	G	0.18
11	NCAM1	rs586903	113110946	175	.13	C	A	0.32
11	NCAM1	rs2303377	113111501	175	.44	G	A	0.44
11	NCAM1	rs605843	113125234	174	.29	C	T	0.20
11	NCAM1	rs2288158	113133676	175	.16	C	A	0.58
11	NCAM1	rs598026	113139250	175	.15	G	A	0.77
11	NCAM1	rs2156485	113143557	174	.25	T	C	0.11
11	NCAM1	rs593217	113153489	175	.45	C	T	0.65
11	NCAM1	rs688011	113154170	175	.31	A	G	0.48
11	NCAM1	rs7103866	113164768	170	.28	T	C	0.71

11	TTC12	rs1893699	113192524	172	.39	C	A	1.00
11	TTC12	rs723077	113194168	175	.45	C	A	1.00
11	TTC12	rs2303380	113200709	175	.36	G	A	0.51
11	TTC12	rs948176	113204481	175	.19	G	A	0.63
11	TTC12	rs2288159	113211329	169	.2	A	C	0.81
11	TTC12	rs719804	113234775	174	.23	G	A	0.40
11	TTC12	rs2282511	113244177	174	.32	T	G	0.30
11	ANKK1	rs877138	113256508	175	.31	C	T	0.29
11	ANKK1	rs4938012	113259654	175	.31	T	C	0.29
11	ANKK1	rs17115439	113264272	174	.33	A	G	0.17
11	ANKK1	rs4938013	113264470	174	.31	A	C	0.29
11	ANKK1	rs4938015	113264644	173	.33	T	C	0.17
11	ANKK1	rs1800497	113270828	175	.2	T	C	0.81
11	DRD2	rs6279	113281073	164	.35	G	C	0.30
11	DRD2	rs1076560	113283688	175	.14	A	C	0.75
11	DRD2	rs2283265	113285536	173	.13	T	G	0.51
11	DRD2	rs2440390	113286878	174	.12	A	G	0.47
11	DRD2	rs2075654	113289066	175	.14	A	G	0.54
11	DRD2	rs1800498	113291588	174	.44	G	A	0.44
11	DRD2	rs2587548	113292212	174	.43	G	C	0.35
11	DRD2	rs1076563	113295909	175	.43	T	G	0.36
11	DRD2	rs1076562	113296008	174	.29	A	G	0.58
11	DRD2	rs1079597	113296286	169	.14	A	G	1.00
11	DRD2	rs1079596	113296619	175	.14	T	C	0.75
11	DRD2	rs1125394	113297185	175	.14	G	A	0.75
11	DRD2	rs2471857	113298339	175	.14	A	G	0.36
11	DRD2	rs7103679	113303674	170	.14	T	C	0.53
11	DRD2	rs4586205	113307129	174	.3	G	T	0.86
11	DRD2	rs4648318	113313389	175	.28	C	T	1.00
11	DRD2	rs11214608	113315355	174	.45	G	A	0.45
11	DRD2	rs4274224	113319452	174	.42	G	A	0.64

11	DRD2	rs4581480	113324474	175	.12	C	T	0.47
11	DRD2	rs4648317	113331532	175	.18	T	C	0.45
11	DRD2	rs4350392	113335717	174	.43	T	G	4.60×10^{-13}
11	DRD2	rs4245149	113338357	175	.18	A	G	0.45
11	DRD2	rs4938019	113341391	175	.18	G	A	0.61
11	DRD2	rs10891556	113352761	168	.21	A	C	1.00
11	DRD2	rs6589377	113355736	175	.3	C	T	0.37
11	DRD2	rs4482060	113358211	170	.37	A	T	0.51
11	DRD2	rs4245150	113364647	175	.3	G	T	0.37
11	DRD2	rs4938023	113374847	175	.29	A	C	0.36
11	DRD2	rs12361003	113380818	175	.35	T	G	0.62
11	DRD2	rs2514218	113392994	175	.27	T	C	0.85
11	DRD2	rs2511515	113397655	175	.31	C	A	1.00
22	COMT	rs737866	19930109	175	.25	G	A	0.07
22	COMT	rs933271	19931407	174	.25	G	A	0.31
22	COMT	rs174675	19934051	174	.25	T	C	0.31
22	COMT	rs5993883	19937638	175	.47	C	A	0.23
22	COMT	rs740603	19945177	169	.45	C	T	0.88
22	COMT	rs165656	19948863	133	.39	G	C	0.72
22	COMT	rs6269	19949952	165	.1	C	T	4.98×10^{-15}
22	COMT	rs2239393	19950428	175	.35	C	T	1.00
22	COMT	rs4680	19951271	175	.42	G	A	0.88
22	COMT	rs4646316	19952132	175	.26	T	C	0.33
22	COMT	rs174696	19953176	174	.24	C	T	0.84
22	COMT	rs9332377	19955692	173	.12	T	C	0.28
23	MAOA	rs5906729	43520371	175	.28	C	G	1.00
23	MAOA	rs1465108	43538209	175	.29	T	C	1.00
23	MAOA	rs5906957	43547310	175	.22	T	C	0.63
23	MAOA	rs909525	43553202	173	.29	G	A	1.00
23	MAOA	rs2235185	43595743	175	.26	T	C	1.00
23	MAOA	rs2072744	43599436	175	.32	A	G	1.00

23	MAOA	rs979605	43601363	174	.28	A	G	1.00
23	MAOA	rs2239448	43602679	175	.27	A	G	1.00
23	MAOB	rs1799836	43627999	175	.4	C	T	0.02
23	MAOB	rs10521432	43633740	175	.23	T	C	1.00
23	MAOB	rs6651806	43688964	175	.23	G	T	1.00
23	MAOB	rs5905512	43726394	174	.47	C	T	1.00

Note. Chr = Chromosome, BP = base pair, MAF = Minor allele frequency, Min = Minor allele, Maj = Major allele.