Preliminary association of both the Dopamine D2 Receptor (DRD2) [Taq1 A1 Allele] and the Dopamine Transporter (DAT1) [480 bp Allele] genes with pathological aggressive behavior, a clinical subtype of Reward Deficiency Syndrome (RDS) in adolescents

Research Article

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Abbreviations: 3-4- dihydroxyphenylacetic acid, (DOPAC); 5-hydroxyindoleacetic acid, (5-HIAA); analyses of covariance, (ANCOVs); ankyrin repeat and kinase domain containing 1, (ANKK1); attention-deficit hyperactivity disorder, (ADHD); brain-derived neurotropic factor, (BDNF); dopamine D2 receptor gene, (DRD2); dopamine transporter gene, (DAT1); dopamine, (DA); Epidemiological Catchment Area, (ECA); monoamine oxidase enzyme, (MAOA); Norepinephrine, (NE); nucleus accumbens, (NAc); Pathological Violent, (PV); Reward Deficiency Syndrome, (RDS); substance use disorder, (SUD)

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Summary

Advances in our knowledge of the neurobiology of aggression have given rise to rational pharmacological treatments for these behaviors. The main biological systems which are known to be involved are certain reward neurotransmitters that include serotonin (5HT), opioid peptides (END), gamma-aminobutyric acid (yABA), and the catecholamines (dopamine [DA] and Norepinephrine [NE]). We hypothesize that pathological aggression in adolescents may in part involve polymorphisms of genes linked to the dopaminergic system. It is our notion that pathological aggression is in part similar mechanistically to other forms of impulsive behaviors such as pathological gambling. By analogy to drug dependence, it has been speculated that the underlying pathology in pathological gambling is a reduction in the sensitivity of the reward system. The potential correlation of both the dopamine D2
receptor gene (DRD2) and the dopamine transporter gene (DAT1) polymorphisms with pathological aggression in adolescents was investigated in a total of 291 subjects. Only eleven Caucasian adolescent subjects were diagnosed to have impulsive-aggressive behavior or pathological aggression. For this study 30 super normal controls were screened to exclude a number of reward deficit behaviors including pathological aggression and were genotyped for the DRD2 gene only (the DAT gene genotyping was not similarly genotyped in the super control sample). In the “super normal control group” only one person out of the 30 individuals genotyped carried the A1/ A2 genotype (3.3%). Additionally, 91 controls were screened to exclude only Attention Deficit Hyperactivity Disorder (ADHD), pathological aggression, alcohol, drug dependence and tobacco abuse. In the present study, 6 out of 11 of the pathological aggressive subjects had the DRD2 A1 allele (55%) 11 out of 11 of the subjects (100%) carried the DAT1 10 allele, whereas 7 out of 11 or 64% carried the 9 allele. When the DRD2 A1 allele (A1/A1 or A1/2) genotype in these subjects was compared to super controls (1/30 or 3.3%) a significant association was observed (Fisher’s exact test p= 0.0006); a similar trend was found with DAT1 480 bp 10/10 genotype when compared to controls (Fisher’s exact test p=0.089). However, when the DAT1 9/10 and 10/10 genotypes were compared with controls a significant association was observed (Fisher’s exact test p= 0.00006). Albeit the small number of subjects, this is the first report on DNA polymorphisms to suggest a role for both the DRD2 and DAT genes in pathological aggressive behavior and warrants further investigation.

I. Introduction

In terms of pathological aggressive behavior a number of neurotransmitter systems (Broderick et al, 1973; Linnoila et al, 1983; Brunner et al, 1993; Muhlenkamp et al, 1995; Yaryura-Tobia et al, 1995) are involved. We and others have hypothesized polygenic inheritance for complex behaviors such as pathological (impulsive) aggression. One major pathway that may play a pivotal role in aggressive behavior should include the dopaminergic system. In this regard, Berton and colleagues recently established in 2006 an essential role for the neurotrophic factor BDNF (brain-derived neurotropic factor) in the mesolimbic dopamine pathway in social defeat stress in mice. BDNF is a key regulator of the mesolimbic dopamine pathway and potentiates dopamine release in the nucleus accumbens (NAc) through activation of the TrkB receptors on dopaminergic nerve terminals (Goggi et al, 2003). Aversive stimuli such as aggression and subordination also activate the mesolimbic dopamine pathway and have been linked to chronic alterations in dopaminergic function (Insel and Fernald, 2004). Dopaminergic abnormalities have been linked to a number of disorders including schizoid-avoidance behavior (Blum et al, 1997), human affective disorders, such as depression, social phobia, post-traumatic stress disorder (Tithonen et al, 1997; Schneier et al, 2002; Keedwell et al,2005) as well psychosis, including paranoid schizophrenia (Aragues et al, 2005). Activation of this neural circuitry has been characterized extensively in relation to drugs of abuse and other addictive behaviors, but the genetics of this system have been less characterized in pathological aggressive behavior especially in adolescents.

It is our notion that pathological aggressive behavior is in part similar mechanistically to other forms of impulsive behaviors such as pathological gambling. By analogy to drug dependence, it has been speculated that the underlying pathology in pathological gambling is a reduction in the sensitivity of the reward system. Studying pathological gamblers and controls during a guessing game using functional magnetic resonance imaging, Reuter and colleagues observed in 2005 a reduction of ventral striatal and ventromedial prefrontal activation in the pathological gamblers that was negatively correlated with gambling severity, linking hypoactivation of these areas to disease severity.

Advances in our knowledge of the neurobiology of pathological (impulsive) aggression have given rise to rational pharmacological treatments for these behaviors. The major biological systems known to be involved are certain reward neurotransmitters which include serotonin (5HT), opioid peptides (END), gamma-aminobutyric acid (gABA), and the catecholamines (dopamine [DA] and Norepinephrine [NE]). Normal aggression can be premeditated (offensive) or impulsive (defensive). We refer to impulsive aggression (or explosive aggression) as pathological when there is little or no provocation and the aggressive behavior is repetitive. For the purpose of this paper, the terms pathological aggression and impulsive aggression will be used interchangeably. Typically, the animal literature refers to normal animal aggression as offensive or defensive. In contrast, the human literature refers to either pathological aggression, which is impulsive, or violent offending, which is often premeditated (Broderick et al, 1973; Linnoila et al, 1983; Brunner et al, 1993; Muhlenkamp et al, 1995; Yaryura-Tobia et al, 1995; Jacobs et al, 2007; Fischer et al, 2007).

A. Serotonin

A large body of data has emerged linking impulsive aggression in humans with low serotonergic function. Yaryura-Tobias and colleagues reported in 1995 higher levels of aggression in adults with low blood levels of serotonin. Linnoila and colleagues reported in 1983 that impulsive aggression was associated with low levels of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid. Moreover, others reported on a Dutch family in which a gene mutation in the monoamine oxidase enzyme (MAOA), resulting in a defect in the breakdown of dopamine, serotonin and norepinephrine, was associated with markedly increased aggressive behaviors in teenagers (Brunner et al, 1993). Moreover, Muenlenkamp and colleagues have reported in 1995 that stimulation of the 5-HT1A, 5-HT1B and 5-HT2 receptors reduces offensive aggression, while defensive aggression is reduced only by stimulation of the 5-HT2 receptor. In muridial rats, 5-HT was higher in the hypothalamus compared to non-muridial animals as well as higher levels of 5-HT in the amygdala. The serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) was also found to be higher in the hippocampus of the muridial rats (Broderick et al, 1973).

B. Catecholamines

In animal studies Haller and colleagues found in 1996 that enhancing catecholamine function by treatment with alpha-2 adrenergic receptor antagonists increased aggressive responses to intruders. Further experiments (Eichelman et al, 1975) in rodents revealed that tryclics and MAO inhibitors, which increased both DA and NE activity, also enhanced aggressive behavior in these animals. In humans, the NE metabolite 3-methoxy-4-

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hydroxyphenylglycol correlated with a positive history of aggressive behavior (Brown et al, 1979) and a positive correlation between aggression and blood levels of phenylethylamine was also found in humans (Sandler et al, 1978). Acute isolation–induced fighting in mice produced a striking “dose–dependent” increase in K_d and V_max for dopamine uptake in mesocortical nerve endings (synaptosomes) but no significant changes for these uptake constraints in nigrostriatal terminals (Hadfield, 1983). Moreover, the dopamine-induced metabolism of 3,4-dihydroxyphenylacetic acid (DOPAC) was significantly lower in muricidal rats compared to nonmuricidal animals. The hippocampus of muricidal rats showed significantly higher DA levels, and higher levels of the NE metabolite homovanillic acid (HVA) were found in the hippocampus of muricidal rats (Broderick et al, 1973). Breese and associates provide evidence to suggest that lack of brain dopamine during development increases the susceptibility for aggression and injurious behavior by influencing D1 dopamine receptor function (Breese et al, 1990). Furthermore, work from Comings and colleagues showed in 1997 a strong association between aberrant drug seeking behavior and polymorphisms of the D1-dopamine receptor gene.

C. Opioid peptides

The role of opioid peptides has also been studied with regard to aggressive behavior and fighting in animals. Beta-endorphin blocked the development of shock–induced fighting, while Naloxone facilitated it but only when shock-fighting occurred at a low rate. The beta-endorphin induced reduction of fighting behavior was blocked by naloxone, suggesting opiate induced receptor mechanisms in aggressive behavior (Tazi et al, 1983). Moreover, Comings and colleagues also associated in 1999 the enkephalinase gene with low amplitude P300 waves, which has been associated with violent offenders (Figure 1 P300 wave map in a violent subject).

D. GABA

GABA is found ubiquitously in the central nervous system; its function is reducing neuronal activity. Eichleman concluded in 1988 that GABA stimulation centrally reduces aggression, but some studies showed a significant percent of patients treated with benzodiazepines becoming more aggressive. Moreover, GABA receptor agonists seem to attenuate heightened alcohol aggressive behavior. It has been suggested that the benzodiazepine chloride ion channel may be a potential anti-aggressive target site (Miczek et al, 1995). Animal studies support a role glutamate in offensive aggressive behavior. Results of a recent study suggest that altered glutamate synthesis and GluR1 receptor expression in specific aggression areas may be involved in adolescent anabolic steroid induced offensive aggression (Fischer et al, 2007).

E. Natural Vs unnatural rewards

Grasping the mechanism of motivated behavior requires an understanding of the neural circuitry of rewards (Robbins and Everitt, 1996), otherwise called positive reinforcers. A positive reinforcer is operationally defined as an event that increases the probability of a subsequent response, and drugs of abuse are considered to be stronger positive reinforcers than natural reinforcers (e.g. food and sex) (Cooper et al, 1995; Epping-Jordan et al, 1998; Wightman and Robinson, 2002). The distinction between “natural rewards” and “unnatural rewards” is an important one. Natural rewards include satisfaction of physiological drives (e.g. hunger and reproduction), and unnatural rewards are learned and involve satisfaction of acquired pleasures such as hedonic sensations (Suhara et al, 2001) derived from alcohol and other drugs, as well as from gambling and other risk-taking behaviors (Hodge et al, 1996, 1998; Robbins and Everitt, 1996).

In discussing RDS, we refer specifically to an insensitivity and inefficiency in the acquired (or unnatural) reward system (Blum et al 1996; Blum and Braverman, 2000; Comings and Blum, 2000). RDS also encompasses the acquired need to escape or avoid negative affects created by repeated cycles of alcohol abuse (Koehnke et al, 2002) and dependence.

In view of this evidence of the role of dopamine and aggressive behavior, we decided to carry out association studies of polymorphisms of the DRD2 and DAT1 genes with pathological aggressive behavior in a small adolescent cohort.

II. Methods

A. Subjects

A total of 291 individuals were carefully accessed in this study at three different institutions, The Brown School, San Marcos, Texas, (N =11). The New York Center, Duarte, California (91). For this study the experimental group consisted of eleven male Caucasian adolescents between the ages of 12 and 19 with an average mean age (+ SD) of 13.87 (+1.40), who were in residential treatment program at the Brown School in San Marcos, Texas. These subjects were selected on the basis of a one-hour structured interview and were all diagnosed to have repetitive, unprompted, impulsive aggressive behavior (pathological aggression), and their DNA was collected for genotyping. Moreover, each subject selected had a 2.5 SD abnormal brain electrical activity during long latency (500 msec) auditory evoked responses compared to an age, sex and handedness matched normal control group measured by the Nicolet® BEAM instrument. Only eleven subjects out of a cohort of over 100 patients attending the Brown School of San Marcos, Texas, met the study criteria. Six of the subjects had, in addition, abnormal (absent) P300 responses to auditory oddball paradigm cognitive evoked response testing. A typical electrical brain map of P300 response in an aggressive subject is presented in Figure 2. These subjects are very difficult to find even in a cohort of compromised mentally disturbed adolescents (Only 11% met the criteria).

The control group consisted of thirty super normal controls. These individuals were selected from a total of 189 individuals attending the PATH Medical Clinic in New York City, for both neurological and non-neurological problems. These individuals were carefully screened to exclude a number of reward behaviors including but not limited to alcoholism, substance use disorder (SUD), smoking behavior, carbohydrate binging, obesity, attention-deficit hyperactivity disorder (ADHD), posttraumatic stress disorder, conduct disorder, antisocial behavior, pathological gambling, aggressive offenses, pathological aggression, deviant sexual behavior, schizoid/avoidant behavioral cluster and other axis 1 and axis 11 mental disorders. These subjects were only genotyped for the DRD2 gene polymorphisms. Those who showed a family history of substance abuse/depedence and other defined reward behaviors (including psychiatric disorders (i.e. schizophrenia or mood disorders) were excluded). At a different time for another study, we also genotyped 91 controls that were screened to exclude only ADHD, alcohol and other drugs of abuse, tobacco abuse and dependence and pathological aggression for the DAT1 gene polymorphisms. The study protocol was approved by the PATH Foundation IRB (registration number IRB00002334) and Ethics Committee and each participant signed an informed consent.

B. Genotyping

Buccal epithelial cells were collected by cotton swabs for DNA isolation. In some subjects a blood sample was obtained for DNA isolation. The construction of primers and methods for both
the DRD2 and DAT genes were previously described by Grandy et al, 1989 and Comings et al, 1996.

1) DRD2 polymorphism: The D2A1 and D2A2 genotyping was performed by hybridization of Southern blots as described previously (Comings et al, 1996). A number of samples were also genotyped by a PCR technique (Comings et al, 1996).

2) DAT1 polymorphism: The DAT1 alleles (VNTR situated at the 3' end of the gene) were determined according to the described procedure of Comings et al, 1996.

C. Statistics

DRD2 gene polymorphisms were classified and assessed as follows: Taq1 A (A1 + {A1/A1 and A1/A2 genotypes} vs. A1- (A2/A2 genotype)). DAT1 VNTR alleles were classified and assessed on the basis of the presence or the absence of the 10-repeat (10/10 or 9/10) vs. the 9 repeat (9/9).

Due to the small sample size of 11 pathological aggression cases, one-tailed Fisher’s exact tests were used to test the association between genotype distribution and diagnosis (pathological aggression vs. control), with p<0.05 considered statistically significant. Since the three tests that were performed were orthogonal, no correction for multiple testing was necessary. 95% confidence intervals based on the binomial distribution were also calculated for each prevalence percentage estimate when possible. Statistical analyses were carried out using Stata 9.0 for Windows.

Figure 1. (A) BEAM of violent and aggressive person, (B) BEAM of non-violent person.

Figure 2. Illustrates the genotypic prevalence of the eleven Caucasian males with pathological aggressive behavior of both the DRD2A1 polymorphism of the dopamine D2 receptor gene and the 10/10 and 9/10 alleles of the dopamine transporter gene (DAT1) in control subjects. The experimental subjects possessing the A1 allele of the DRD2 gene was compared against the 30 super controls and the prevalence of the 10/10 and 9/10 DAT1 alleles of the experimental subjects were compared against the 91 screened controls.

III. Results
We found the super normal controls to carry the A1 allele in only the person out of 30 (1/30) for an A1+ rate of 3.3% with 95% c.i. of (0.1, 7.2). The A1+ found in minor form and genotype data from over 3,329 results occurs in approximately 30 percent of the unscreened global population (Noble, 2003). It is to be noted that the A1- is a major allele found in approximately 66% of the unscreened American population. Additionally, we found the less rigorous 91 controls to carry the DAT1 10/10 at 37.4% with 95% c.i. of (27.4, 48.1); the 9/10 at 43.9% with 95% c.i. of (36.6, 51.8) and the 9/9 was found in 4.8% with 95% c.i. of (7.0, 21.9). Based on genotype data for the DAT1 gene on 3,080 subjects, the 480bp 10/10 allele occurs in approximately 55% of the unscreened American population; the 9/10 occurs in approximately 38% of unscreened Americans; and the rare 9/9 allele occurs in 7% of unscreened Americans (Comings et al, 1996).

Eleven Caucasian adolescent subjects were diagnosed to have impulsive-aggressive behavior or pathological aggression. For this study 30 super normal controls were screened to exclude a number of reward deficit behaviors including pathological aggression and genotyped for the DRD2 gene only. Additionally, 91 controls were screened to exclude only ADHD, pathological aggression, alcohol, drug dependence and tobacco abuse. While six out of 11 of these subjects, all of whom had an absence of P300 responses, had the DRD2 A1 allele for a prevalence of 54.5% with 95% c.i. of (23.4, 83.3), 11 out of 11 of the subjects carried the DAT1 10 allele for a prevalence of 100% (95% c.i. cannot be calculated), whereas seven out of 11 carried the 9 allele for a prevalence of 63.6% with 95% c.i. of (30.8, 89.1). When the DRD2 A1 (A1/A1 or A1/A2) genotype in these subjects were compared to the super controls (1/30 or 3.3%) a significant association was observed (Fisher’s exact test ps 0.0006); a similar trend was found with DAT1 480 bp 10/10 genotype when compared to controls (Fisher’s exact test p=0.089). However, when the DAT1 9/10 and 10/10 genotypes were compared with controls a significant association was observed (Fisher’s exact test ps 0.00006). (Figure 2).

The below topographical brain map (Figure 1) of a pathological aggressive and violent substance abusing teenager, is similar for aggressive and violent substance abuse offenders in treatment at the PATH Medical Clinic over a ten year period (Blum and Braverman, 2000).

IV. Discussion

This paper presents the first study to demonstrate a putative positive association of dopaminergic polymorphisms and pathological aggressive behavior in adolescents. While these results are preliminary due to the low number of experimental subjects, the careful selection and exclusion criteria, the comprehensiveness of the research methodology and the specificity of the genetic biomarkers, provides strong insights into the etiology of pathological aggression and merits further investigations.

It is well documented that aggressive behavior represents a very complex phenotype. The first question that we must raise is – What constitutes an adequate sample of persons with a given psychiatric diagnosis such as aggression and pathological aggression, and what should we demand of our control groups if we are interested in testing population–based associations? For population–based studies in which the investigator requires a representative control sample, the obvious limitation of this strategy is that this sample may contain individuals with the same disease as that being studied in the experimental group, potentially reducing the power to detect differences between the groups. Thus, removing these confounding cases from the control group may improve chances of finding significant differences between experimental and control groups, but risks the lack of representativeness in the control group. Even the use of stratified samples (weighting samples) may not be good enough (Hill and Neiswanger, 1997).

In the case of finding a “pure” phenotype, especially in the psychiatric arena, we really do not know if nature carved out the psychiatric disorders in the same fashion as is seen in DSM-IV, -genes for behavioral tendencies (anxiety, impulsivity, compulsivity, but not aggression, aggressiveness) may be the ultimate source for our understanding of psychiatric disorders.

One major problem as to recognize that when we consider the pathological aggression phenotype it may be represented by some combination of a number of behavioral tendencies. In this regard, when we consider reward dependence behaviors an emerging concept called Reward Deficiency Syndrome (RDS) (mentioned earlier) may help define this complex array of behaviors (Blum et al, 1996; Comings and Blum, 2000). RDS broadly defines a common genetic tendency whereby the individual may be predisposed to a number of addictive, impulsive and compulsive behavioral tendencies. The need for homogeneity in the affected phenotype is important not only for population-based association studies but also for linkage analysis. Under the RDS concept we are dealing with a list of behavioral tendencies including dependence on alcohol, psychostimulants (cocaine), opiates, marijuana, nicotine (smoking), carbohydrates (sugar binging), pathological gambling, sex addiction, premeditated aggression and pathological aggression, all sharing some genes in common (Hill, 1998). While there are polypgenes involved, there is close similarity in terms of all of these substances and behaviors that induce presynaptic dopamine release at the n. accumbens. A screened control group is essential for uncovering population-based associations where the disease in question may be very common. Why is this so? We know that approximately one-third of the population meet lifetime criteria for common psychiatric disorders according to the results of the Epidemiological Catchment Area (ECA) survey. Since these are polygenic disorders requiring a threshold number of polygenes, unaffected individuals in the population also carry some of these genes. The dopamine D2 receptor gene (A1 allele) is present in about one-third of unscreened Americans.

The use of a super control has been criticized by some on the grounds that their relatives will have rates of comorbid disorders lower than that in the general population and may produce spurious co-aggregation of disorders within families. This argument is valid only if the same psychopathology which is removed from the control group is not excluded from among the probands and their relatives. This provides the rational to encourage others to begin to carefully select true controls especially when dealing with complex traits (Hill, 1998).

We believe that our preliminary finding of an association of both the DRD2 and DAT1 polymorphisms provide the first DNA evidence that these two dopaminergic genes play a significant role in pathological aggression. In support of these findings the DRD2 A1 alleles have been found to be associated with not only with personality disorders, (Noble et al, 1998; Mulde, 2002) but with alcoholism (Blum et al, 1990) and dopamine density (Noble et al, 1991; Hetiata et al, 1994). Furthermore, dopamine transporter receptor sites are significantly increased in violent compared to non violent alcoholics (Tikkonen et al 1995). Under the RDS concept, a significant association has been found between the DRD2 A1 allele and pathological schizoid/avoidant cluster (Blum et al,
1997). While schizoid/avoidant individuals initially tend to be languid, remote, passionless, depersonalized, conflicted, hypersensitive, phobic, and self-deserting, the literature indicates these people tend to alleviate these dysphonic symptoms and seek out pleasure through outrageous acts of aggression with a pervasive pattern of social discomfort followed by substance use disorder. It is noteworthy that Pontius, reported in 1996 on a condition called ‘limbic psychotic trigger reaction’, supporting the link between limbic dysfunction, unexplained murders, and schizoid/avoidant personality traits.

As we see from the data presented herein, genes play a role in aggressive and violent behavior (Clark and Grunstein, 2000). Studies at the University Of Wisconsin (Bouchard and Loehlin, 2002), using identical twins raised in different families, who had parallel lives, showed that about half of human behavior (including aggression, sexuality, mental function, eating disorder, alcoholism and drug abuse or generalized RDS) can be accounted for by genes (Bouchard and Loehlin, 2002). Very few behaviors depend upon a single gene. Complexes of genes (polygenic) drive most of our heredity-based actions. However, it is also important to distinguish between pathological aggression and violent offenses, since the former represents impulsive aggression and the latter is generally premeditated. These two potentially distinct behaviors are not understood but may warrant additional research.

Certainly abnormal functioning of these brain systems can be due to specific genetic factors interacting with environmental factors such as abuse of various psychoactive substances, particularly alcohol and stimulants. In this regard, it has been shown that these individuals may have a reduced number of dopamine D2 receptors (Noble et al, 1991; Hietala et al, 1994) and a high number of dopamine transporter sites (Tihonen et al, 1995). Certainly the finding of hypodopaminergic function as discovered in pathological gambling (Reuter et al, 2005), an example of a RDS behavior, helps us understand the potential driving force of some to induce activation of the dopamine system. Pathological aggression and violent offending behaviors may induce such dopaminergic activation thereby reducing a pathological reward deficiency. Understanding the interaction of these components is likely to lead to better treatment.

Regarding the polymorphism association, a major difficulty with an association of the DRD2 TaqA1 allele with any reward dependent behavior including alcoholism and in this case pathological aggression, is that the TaqA1 A polymorphism is located more than 10kb downstream from the coding region of the DRD2 gene (Johnson, 1996) and a mutation at this site would not be expected to lead to any structural change in the dopamine receptor. The most likely explanation for an association is that the TaqA1 A polymorphism is in linkage disequilibrium with an upstream regulatory element, or a 3’ flanking element, or another gene which confer susceptibility to RDS behaviors. Several linkage disequilibrium studies have found strong linkage disequilibrium between the TaqA1 allele and the Taq1B allele and the SSCP1 allele (Blum et al, 1993; Goldman et al, 1993; O’Hara et al, 1993; Johnson 1996; Hill et al, 1993). As we have pointed out, the dopamine D2 receptor has been implicated extensively in relation to alcoholism, SUD, nicotine dependence, anxiety, memory, glucose control, pathological aggression, pathological gambling, and certain sexual behavior all of which are RDS behaviors. The most frequently examined polymorphism linked to this gene is the TaqA1 restriction fragment length polymorphism, which has been associated with a reduction in D2 receptor density. In a recent study, within the 10kb downstream region of the TaqA1 RFLP, Neville and associates identified a novel kinase gene, named ankyrin repeat and kinase domain containing 1 (ANKK1), which contains a single serine/threonine kinase domain and is expressed at low levels in placenta and whole spinal cord RNA. There have been no studies to date that linked the presence of this gene to brain tissue. This gene is a member of an extensive family of proteins involved in signal transduction pathways. The DRD2 Taq1A allele is a single nucleotide polymorphism (SNP) that causes an amino acid substitution within the 11th ankyrin repeat of ANKK1 (p. Glu713Tyr), which while unlikely to affect structural integrity, may affect substrate-binding specificity. If this is the case, then changes in ANKK1 activity may provide an alternative explanation for previously described associations between the DRD2 gene and RDS behaviors (Neville et al, 2004).

V. Conclusion
Thus, these results preliminarily support the concept that dopaminergic genes, in particular the DRD2 and DAT1 polymorphisms, are significantly associated with the reward–dependent traits (Blum et al 1996; Blum and Braverman, 2000; Comings and Blum, 2000) such as pathological aggression and warrants further research (Chen et al, 2005). Moreover, these results may have direct implications for both the diagnosis and targeted treatment of pathologically aggressive and violent offending behaviors.

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