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The DRD2 gene 957C>T polymorphism is Associated with Post Traumatic Stress Disorder in War Veterans

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Abstract

Background: Variations in genes related to the dopaminergic pathway have been implicated in neuropsychiatric disorders such as schizophrenia, substance misuse, Alzheimer's disease and Post Traumatic Stress Disorder (PTSD). A single nucleotide polymorphism (SNP) (957C>T) and a deletion polymorphism (-141delC) in the *DRD2* gene and a SNP (*Taq*1A) in a gene directly downstream of *DRD2* have all been implicated in dopamine functioning in the brain.

Methods: To test the importance of these three polymorphisms in PTSD susceptibility, a genetic screen was performed in 127 war veterans diagnosed with PTSD and 228 control individuals without a history of PTSD.

Results: No significant association was found between PTSD and the *Taq*1A or -141delC polymorphisms. However, a significant association was observed with PTSD and the 957C>T polymorphism. PTSD individuals were more likely to carry the C allele compared to the controls ($P = 0.021$).

Conclusions: Our findings suggest that the 957C>T polymorphism in the *DRD2* gene is one of the genetic factors for susceptibility to PTSD.

Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric condition that occurs following exposure to a life threatening experience. PTSD has been reported to occur in about 8% of all Americans at some stage in their life with women twice as likely as men to develop the disorder (Kesssler 1995). A common cause is stress after military combat but violent personal assaults, serious accidents and terrorist incidents can also lead to PTSD. Individuals suffering from PTSD often relive the traumatic experience through flashbacks and nightmares, have difficulty sleeping, have problems with concentration and memory and are often easily startled or frightened. PTSD is a highly debilitating condition with individuals frequently suffering poor relationships, self destructive behaviors, and hallucinations, feelings of isolation or hopelessness, and aberrant emotions ranging from numbness to anger. While PTSD is considered an anxiety disorder it is often comorbid with major depression and has recently been shown to share a common genetic liability (Koenen et al.). Biological symptoms are also seen with PTSD, including alterations in the central and autonomic nervous systems resulting in decreased processing and integration of memory (Kesssler 1995). Hyper-arousal of the sympathetic nervous system is associated with PTSD and is characterized by sleep abnormalities. Other biological characteristics of PTSD include increased thyroid function, lower cortisol but increased adrenaline and nor-adrenaline blood concentrations (Kesssler 1995).

Familial and twin studies suggest that there is a genetic predisposition to PTSD. For example, studies of twin males in military combat from the Vietnam war found that genetic factors significantly contribute to PTSD susceptibility (Koenen et al. 2002; True et al. 1993). The risk of developing PTSD following combat trauma in Vietnam was

also found to be higher in individuals with a family history of depression (True et al. 1993). Similarly, in Cambodian refugees PTSD was found to cluster in families suggesting high heritability (Sack et al. 1995).

The aetiology of PTSD has been associated with brain dopaminergic activity. Polymorphisms of the *DRD2* (dopamine D2 receptor) gene (Klimek et al. 2002; Lawford et al. 2006; Schneier et al. 2000) which have been associated with differences in DRD2 density (Abi-Dargham et al. 2000; Seeman and Kapur 2000), reduced D2 receptor binding (Noble et al. 1991; Thompson et al. 1997) and dopamine synthesis (Laakso et al. 2005) make *DRD2* a good candidate for a significant genetic contribution to PTSD. In addition, a synonymous polymorphism, 957C>T (rs6277) (Hanninen et al. 2006; Hoenicka et al. 2006; Lawford et al. 2005) and a deletion polymorphism, 141del C (rs1799732) (Ohara et al. 1998) in the *DRD2* gene have been found to be associated with schizophrenia, which shares some of the characteristics of PTSD and is also believed to result from dysregulation of dopamine. Specifically, this mutation has been shown to affect mRNA stability and protein translation of the receptor (Duan et al. 2003) and affects striatal dopamine D2 binding in healthy subjects (Hanninen et al. 2006). The T allele is associated with decreased *DRD2* mRNA stability, decreased translation of *DRD2* mRNA, and diminished dopamine induced up-regulation of D2 receptors (Hirvonen et al. 2005).

Another polymorphism situated in the *DRD2* region known as *Taq*IA (rs1800497) is a non-synonymous G/A polymorphism found within the coding region of the ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene which is located downstream of the *DRD2* (Neville et al. 2004). In a study of harmful drinkers, our group found that

those who were also diagnosed with PTSD were more likely to have the A1 (A) allele (Young et al. 2002). A similar association has also been shown with schizophrenia (Dubertret et al. 2004). I A is a non-synonymous G/A polymorphism found within the coding region of the ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene which is located downstream of the *DRD2* (Neville et al. 2004). The polymorphism is located in a putative substrate binding domain and results in a Glu713Lys substitution which has been suggested to alter substrate-binding specificity (Neville et al. 2004). The A1 (A) allele of the *Taq*IA polymorphism is associated with increased striatal activity of L-amino acid decarboxylase, the final enzyme involved in the biosynthesis of dopamine, thus possibly indicating increased dopamine synthesis (Laakso et al. 2005).

As depression and anxiety disorders are associated with differences in receptor binding (Abi-Dargham et al. 2000; Klimek et al. 2002; Noble et al. 1991; Schneier et al. 2000; Seeman and Kapur 2000) and a genetic link exists between these disorders and PTSD, we postulate that -141del C and 957C>T polymorphisms in *DRD2* and the *Taq*IA polymorphism in *ANKK1* could be associated with increased PTSD susceptibility.

Methods

Patients and Participants

One hundred and twenty seven unrelated male Caucasian patients diagnosed with PTSD using DSM IV criteria were recruited through the Greenslopes Private Hospital for the study. All subjects were Vietnam combat veterans who had served in the Australian Armed Forces. None were being treated with psychotropic medications. Patients were excluded from the study if they had a diagnosis of psychosis, bipolar disorder, obsessive compulsive disorder, or organic brain syndrome including dementia. All subjects had

sufficient comprehension of English and could understand the administered questionnaires.

Patients were assessed for PTSD by a consultant psychiatrist or a senior psychiatric registrar using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Furthermore, every patient exceeded the clinical cut-off score of 94 on the Mississippi Scale for combat-related PTSD (Keane et al. 1988). Patient clinical history and demographic data including ethnic background were also obtained.

After the procedure had been fully explained, all participants provided written informed consent. They were able to terminate their involvement at any time during the interview without prejudice. Institutional ethics approval was obtained from the Greenslopes Private Hospital.

Two hundred and twenty eight unrelated Caucasian, representative of the general population were also collected as controls.

Genotyping

DNA was extracted from blood using standard techniques and subsequently used as a template for determination of *DRD2* genotypes. Genotyping for the 957C>T polymorphism was performed by kinetic real-time PCR using the Applied Biosystems 7000 sequence detection system (Applied Biosystems, Foster City, CA, USA). Allele specific forward primers were designed for the C allele (5′-ATGGTCTCCACAGCACTCTC-3′), and the T allele (5′-ATGGTCTCCACAGCACTCTT-3′) in addition to a common reverse primer (5′-

CATTGGGCATGGTCTGGATC-3′). A total of 5-10 ng of genomic DNA was amplified in 1 × SYBR green PCR master mix (Applied Biosystems) containing 0.4 μM of allele specific forward primer and 0.4 μM of common reverse primer in a 25 μL volume. Amplification conditions were: 50°C for 2 min, 95°C for 10 min, followed by 40 cycles of 95°C for 15s and 60°C for 1 min. A cycle time (C_t) value was obtained by setting the threshold during geometric phase of amplification and scored relative to the ΔC_t generated between the matched and mismatched primer pairs.

*Taq*IA genotyping was performed by restriction fragment length polymorphism (RFLP) analysis of PCR products. A genomic sequence of 501 bp of the coding region of *ANKK1* was amplified by PCR using the forward primer 5′-GCACGTGCCACCATACCC-3′ and the reverse primer 5′-TGCAGAGCAGTCAGGCTG -3′. A total of 5-10 ng of genomic DNA was amplified in a PCR master mix containing 0.2 μM of forward primer and 0.2 μM of reverse primer, 1x PCR buffer, 1.5 mM $MgCl_2$, 200 μM dNTPs and 1 unit of Platinum *Taq* DNA Polymerase (Invitrogen) in a 25 μL volume. Amplification conditions were: Step 1: 94°C for 4 min, Step 2: 94°C for 30 s, Step 3: 68°C for 30 s, Step 4: 72°C for 30 s, Steps 2-4 were repeated by 40 cycles followed by 72°C for 3 min. Amplified PCR fragments were digested with *Taq*I restriction enzyme (New England Biolabs) and digested fragments were visualized via agarose gel electrophoresis.

Determination of -141delC genotype was performed by RFLP analysis of PCR products. A genomic sequence including 284 bp from the 5′-flanking region and 274 bp from exon 1 of *DRD2* was amplified by PCR using forward primer 5′-

ACTGGCGAGCAGACGGTGAGGACCC-3′ and reverse primer 5′-TGCGCGCGTGAGGCTGCCGGTTCGG-3′. A total of 5-10 ng of genomic DNA was amplified in a PCR master mix containing 0.2 μM of forward primer and 0.2 μM of reverse primer, 1x PCR buffer, 1.5 mM $MgCl_2$, 200 μM dNTPs, 2x enhancer solution (Invitrogen) and 1 unit of Platinum *Taq* DNA Polymerase (Invitrogen) in a 25 μl volume. Amplification conditions were: Step 1: 95°C for 3 min, Step 2: 95°C for 30 s, Step 3: 68°C for 30 s, Step 4: 72°C for 30 s, Steps 2-4 were repeated 40 times followed by a final 72°C step for 2 min. Amplified PCR fragments were digested with *Bst*NI restriction enzyme (New England Biolabs) and digested fragments were visualized via agarose gel electrophoresis.

Statistical Analysis

For each polymorphism, a homogeneity χ^2 analysis was employed to test the hypothesis of homogeneity of allele frequency distributions between PTSD and control populations. An odds ratio with 95% confidence interval (CI) was also calculated. Genotype frequencies were similarly compared between PTSD and control populations. However, where an allele was found to be associated with PTSD, an extended Mantel-Haenszel test was performed to test for a trend to PTSD with increasing copy number (0, 1, or 2) of the allele. Odds ratios were calculated relative to the homozygote for the non-associated allele and population attributable fractions calculated. The calculations for attributable risk were done using genotypes counting the presence of the C allele as a risk factor. All statistics were carried out using the epidemiological software Compare2 v1.25 (Abramson 2004).

Results

Three polymorphisms in the *DRD2* region were genotyped and investigated for an association with PTSD. The 957C>T polymorphism showed a significant association with PTSD at the allele level ($P = 0.021$, Table 1). The C allele was found at a higher frequency in the PTSD patients (51.7%) compared to the controls (42.5%). The odds ratio (OR) of having PTSD when an individual has the C allele was 1.45 (confidence interval 1.04-2.01). The genotypes of both groups are displayed in Table 2. A significant trend in susceptibility to PTSD was found with respect to increasing C alleles in genotypes ($P = 0.021$). The odds of an individual with PTSD having the CC genotype (rather than the TT genotype) are twice that of the controls ($P = 0.041$). Using Compare2 v1.25 software, attributable fraction was calculated using genotypes counting the presence of the C allele as a risk factor. The attributable fraction, which is the proportion of cases in the study population that would not have occurred had the risk factor (risk allele) not been present, is a useful measure to quantify the impact of the allele on the development of PTSD (Lappalainen et al. 2002). The analysis revealed 14% of the susceptibility to PTSD could be attributed to having the CC genotype of the 957C>T *DRD2* polymorphism.

No association with PTSD was observed for the *Taq*IA or -141delC polymorphisms at the allele (Table 1) or genotype level (Table 2). Both PTSD and control groups were determined to be in Hardy-Weinberg equilibrium based on the respective allele frequencies of each group.

Discussion

This is the first study reporting an association with the *DRD2* 957C>T polymorphism and PTSD. The C allele of the *DRD2* 957C>T polymorphism was found to be significantly associated with the disorder. PTSD individuals were more likely to carry

the C allele compared to healthy controls. Fourteen percent of the susceptibility to PTSD could be attributed to having the CC genotype of the *DRD2* polymorphism. Our results suggest that the 957C>T polymorphism contributes to the genetic susceptibility to PTSD.

Earlier studies have found that dopaminergic innervation of the prefrontal cortex is highly sensitive to both acute and chronic stress (Deutch and Roth 1990). Our results support the hypothesis that a defect in the central dopaminergic pathway contributes to post-traumatic symptomatology (Deutch AY 1995). A polymorphism in the *DRD2* receptor which is central to the dopamine system could result in increased production of dopamine thus increasing the risk of psychopathology consequent to traumatic exposure.

Our data fail to support an allelic or genotypic association between the *Taq*IA polymorphism of the *ANKK1* gene and PTSD. These results do not follow the findings by Comings et al. (Comings et al. 1996) that the A1 allele is associated with PTSD. Of 37 Vietnam veterans from an addiction treatment unit who had been diagnosed with PTSD, 22 (59.5%) carried the A1 allele. This compared with only 1 of 19 (5.3%) carrying the A1 allele among individuals who did not have PTSD (Comings et al. 1996). Our results are, however, similar to those of Gelernter et al. (Gelernter et al. 1999) who also found no association between *Taq*IA and PTSD. A possible explanation for this is the nature of the control population used by Comings et al. While Gelernter et al. and our group used random control populations, Comings et al. used Vietnam veterans who had not developed PTSD. Interestingly, our group has previously demonstrated an association between the A1 allele and PTSD (P = 0.004)

but also showed that this was almost entirely as a consequence of a very significant association of A1 with a subgroup of PTSD patients designated as “harmful drinkers” (P = 0.00017). Both PTSD populations studied by Gelernter et al. and Comings et al. were similar in that all or almost all were comorbidly drug or alcohol dependent.

In non-clinical subjects, a significant relationship has been reported between dopamine D2 receptor binding and depression (Kestler et al. 2000). Also, subjects with schizophrenia treated with typical antipsychotic drugs show a worsening of depressive symptoms with increasing dopamine D2 receptor occupancy (Bressan et al. 2002). Similarly, it has been shown that in patients with schizophrenia treated with the atypical antipsychotics, olanzapine or risperidone, high dopamine D2 receptor occupancy was related to the subjective experience of depression (de Haan et al. 2000). Future studies should further investigate the C957C>T as a risk for PTSD with comorbid depression.

The current study recruited male war veterans only and the results may not be generalized to females or individuals who were exposed to trauma other than combat (for example, trauma related to sexual abuse). Stein et al. (2000) (Stein et al. 2000) identified gender differences in susceptibility to PTSD. Women were found to be at a significantly increased risk for PTSD following exposure to serious trauma. A recent study also observed gender differences in the sensitivity to PTSD (Breslau and Anthony 2007). Results found that the relative risk estimate for a second traumatic event was significantly higher in woman compared to men. The age range of patients was also restricted and there was a period of several decades between traumatic exposure and recruitment for this research. This study does not rule out population stratification and therefore our result needs be confirmed by independent replication in a Caucasian group

as well as defined ethnic groups. The sample size for the PTSD population in our study was small and the association will need to be confirmed independently, preferably using a larger sample size of PTSD patients. However, a *P*-value of 0.021 is encouraging using unselected controls as a more significant association is likely to be found using controls screened for lack of exposure to a traumatic event. In this study we used a control population drawn from a normal population who had possibly been exposed to a traumatic event. Using a general population as controls we were able to calculate attributable risk and conclude that 14% of the susceptibility to PTSD could be attributed to having the CC genotype. We did not adjust our p-values for multiple testing as the validity of this technique is controversial (Perneger 1998). Therefore our significant association must be seen as exploratory and further replication is required. Further studies should also employ a control group which is characterised by combat exposure but who do not have PTSD (Bachmann et al. 2005).

In conclusion, considerable evidence emphasizes the importance of dopamine D2 receptor function in both anxiety and depression. This study supports these findings, by reporting for the first time that the 957C allele of the *DRD2* gene is associated with PTSD in Vietnam War veterans. These findings suggest that genetic variation in the dopaminergic pathway may play an important role in the response to stress in humans. Further investigation of the 957C>T *DRD2* polymorphism in anxiety and depression may improve understanding of the pathophysiology of these disorders and may eventually lead to targeted pharmacogenomic treatment strategies.

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TABLE 1. **Allele frequencies of 957C>T, *Taq*I A and –141delC polymorphisms of the *DRD2* region in patients with post traumatic stress disorder (PTSD) compared to controls.**

Group	*n*	Allele frequency		χ^2	*P*	Odd's Ratio (95% CI[a])
957C>T		**C (%)**	**T (%)**			
Control	452	192 (42.5)	260 (57.5)	5.34	0.021	1.45 (1.04 – 2.01)
PTSD	240	124 (51.7)	116 (48.3)			
***Taq*I A**		**A1 (%)**	**A2 (%)**			
Control	446	77 (17.3)	369 (82.7)	2.80	0.094	1.39 (0.93 – 2.07)
PTSD	254	57 (22.4)	197 (77.6)			
–141delC		***Del* (%)**	***Ins* (%)**			
Control	424	48 (11.3)	376 (88.7)	0.71	0.40	0.78 (0.42 – 1.42)
PTSD	198	18 (9.1)	180 (90.9)			

[a] Fisher's exact confidence interval.

TABLE 2. Genotype frequencies of 957C>T, *Taq*I A and –141delC polymorphisms of the *DRD2* region in patients with post traumatic stress disorder (PTSD) compared to controls.

Group	*n*	Genotype frequency			χ^2 (*P*)
957C>T		**C/C (%)**	**C/T (%)**	**T/T (%)**	
Control	226	40 (17.7)	112 (49.6)	74 (32.7)	5.37 * (0.068)
PTSD	120	32 (26.7)	60 (50.0)	28 (23.3)	5.33 [a] (0.021)
Odds Ratio[b]		2.114	1.493	1.000	
		P = 0.041	*P* = 0.324		
Attributable Fraction[c] ±SE		14.05 ± 5.71%	14.68 ± 10.64%		
		P = 0.007	*P* = 0.084		
***Taq*I A**		**A1/A1 (%)**	**A1/A2 (%)**	**A2/A2 (%)**	
Control	223	8 (3.5)	61 (27.4)	154 (69.1)	3.67 * (0.160)
PTSD	127	5 (3.9)	47 (37)	75 (59.1)	2.79 [a] (0.095)
–141delC		***Del/Del* (%)**	***Del/Ins* (%)**	***Ins/Ins* (%)**	
Control	212	4 (1.9)	40 (18.9)	168 (79.2)	0.74 (0.691) [d]
PTSD	99	1 (1)	16 (16.2)	82 (82.8)	

* Likelihood-ratio χ^2 test .

[a]Mantel-Haenszel χ^2 test for trend.

[b] With respect to homozygous genotype of allele not associated with schizophrenia

[c] The proportion of PTSD rate that can be attributed to having 1 or 2 copies of the susceptibility allele. Assumes genotype frequencies in controls are representative of the population and that the odds ratio is an accurate estimate of risk.

[d] Likelihood-ratio χ^2 test .At least one cell has an expected frequency of < 5