A novel *DRD2* SNP associated with schizophrenia predicts age of onset: HapMap tag-SNP analysis

Joanne Voisey[a]*, Christopher D. Swagell[a], Ian P. Hughes[a], Bruce R. Lawford[a,b], Ross McD. Young[a], C. Phillip Morris[a]

Running Title: DRD2 association with schizophrenia

[a]Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia. Tel: +61 7 31386100; Fax: +61 7 31386030.

[b]Division of Mental Health, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia. Tel: +61 7 36368704; Fax: +61 7 36368772.

***Corresponding author**: Joanne Voisey

Institute of Health and Biomedical Innovation,

Queensland University of Technology,

Brisbane, Queensland, Australia.

Ph: 61 7 31386261

Fax: 61 7 31386030

Email: j.voisey@qut.edu.au

Author contacts:

Dr Joanne Voisey, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia. Ph: 61 7 31386261 Fax: 61 7 31386030 Email: j.voisey@qut.edu.au

Dr Christopher Swagell, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia. Ph: 61 7 31386261 Fax: 61 7 31386030 Email: Swagell, cswagell@hotmail.com

Ian P. Hughes, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia. Ph: 61 7 31386261 Fax: 61 7 31386030 Email: i.hughes@uq.edu.au

Bruce R. Lawford, Division of Mental Health, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia. Tel: +61 7 36368704; Fax: +61 7 36368772, Email: Bruce_Lawford@health.qld.gov.au

Ross McD. Young, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia. Ph: 61 7 31386261 Fax: 61 7 31386030 Email: rm.young@qut.edu.au

C. Phillip Morris, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia. Ph: 61 7 31386261 Fax: 61 7 31386030 Email: p.morris@qut.edu.au

Abstract

Background: Dopamine D2 receptor (DRD2) is thought to be critical in regulating the dopaminergic pathway in the brain which is known to be important in the aetiology of schizophrenia. It is therefore not surprising that most antipsychotic medication acts on the Dopamine D2 receptor. DRD2 is widely expressed in brain, levels are reduced in brains of schizophrenia patients and *DRD2* polymorphisms have been associated with reduced brain expression. We have previously identified a genetic variant in *DRD2*, rs6277 to be strongly implicated in schizophrenia susceptibility.

Methods: To identity new associations in the *DRD2* gene with disease status and clinical severity, we genotyped seven single nucleotide polymorphisms (SNPs) in *DRD2* using a multiplex mass spectrometry method. SNPs were chosen using a haplotype block-based gene-tagging approach so the entire *DRD2* gene was represented.

Results: One polymorphism rs2734839 was found to be significantly associated with schizophrenia as well as late onset age. Individuals carrying the genetic variation were more than twice as likely to have schizophrenia compared to controls.

Conclusions: Our results suggest that *DRD2* genetic variation is a good indicator for schizophrenia risk and may also be used as a predictor age of onset.

Keywords: schizophrenia; genetics; polymorphism; dopamine pathway; Dopamine D2 receptor

Introduction

Schizophrenia is a severe psychiatric illness affecting one percent of the population. The genetic risk for schizophrenia is high with some studies predicting up to 80% heritability (McGuffin and Gottesman, 1999; Sullivan *et al.*, 2003). The aetiology of schizophrenia has been associated with brain dopaminergic activity. The dopamine D2 receptor (*DRD2*) gene is located on chromosome 11q22-23 (Grandy *et al.*, 1989) and is thought to play a pivotal role in the dopamine pathway. A genome-wide linkage meta-analysis has also implicated *DRD2* in risk for schizophrenia (Lewis *et al.*, 2003). We have previously reported the 957C-allele of a *DRD2* polymorphism (rs6277) to be significantly associated with schizophrenia (Lawford *et al.*, 2005). Several studies have confirmed this association (Betcheva *et al.*, 2009; Dubertret *et al.*, 2010; Fan *et al.*, 2010; Hanninen *et al.*, 2006; Hoenicka *et al.*, 2006) including a meta-analysis (Monakhov *et al.*, 2008). The T-allele of rs6277 polymorphism has been shown to be associated with decreased *DRD2* mRNA translation and stability as well as reduced dopamine-induced up-regulation of D2 receptors (Duan *et al.*, 2003). In healthy individuals the T-allele is also associated with increased striatal D2 receptor binding (Hirvonen *et al.*, 2005).

There have also been other *DRD2* polymorphisms found to be associated with schizophrenia including the well studied deletion polymorphism rs1799732 in the promoter of *DRD2*. Functional studies have shown that it is associated with lower *DRD2* promoter activity (Arinami *et al.*, 1997). A non-synonymous polymorphism rs1801028 was one of the first polymorphisms showing association with schizophrenia (Arinami *et al.*, 1994) but other studies have failed to replicate this result. Interestingly, a meta analysis did support the association (Glatt *et al.*, 2003).

In summary a number of polymorphisms in *DRD2* have been identified that are associated with schizophrenia but their individual effects on risk for schizophrenia are small. To identify novel polymorphisms associated with schizophrenia and replicate previous association studies, seven SNPs in *DRD2* were selected that mark haplotype blocks, covering the entire *DRD2* gene. Following genotyping in an Australian population these SNPs were analysed for association with schizophrenia.

Materials and Methods

Participants

The study included 157 Caucasian schizophrenia patients and 250 unrelated Caucasian controls. Subjects were aged between 18 and 65 years. Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (American Psychiatric Association, 1994) diagnosis of schizophrenia was confirmed by at least two independent psychiatrists. These patients had never been diagnosed with other psychiatric disorders, including schizoaffective disorder, major depressive episode with psychotic features, or bipolar disorder. No patients were treated with antidepressants, anxiolytic agents, or mood-stabilizing psychotropic medications and all were maintained on a constant dose of antipsychotic medication for a minimum of three weeks. There were 23 females and 134 males in the group diagnosed with schizophrenia with a mean age of 36.2 years (s.d. $\pm$ 12.1 years). The mean age of patients at first diagnosis (onset of psychotic symptoms) was 23.2 years (s.d. $\pm$ 7.3 years). They were being treated at the Royal Brisbane and Women's Hospital, The Park Psychiatric Unit, and the Valley Community Psychiatric Centre. The clinical sample was composed of 65 inpatients and 92 outpatients. All patients were administered the Positive and Negative Symptom Scale (PANSS) (Peralta and Cuesta, 1994) to assess severity of psychotic features. The PANSS total mean score was 45.13, SD. 13.69. This clinical sample was a group who had lived with schizophrenia for an average of 13 years since diagnosis continued to experience positive and negative symptoms despite treatment with antipsychotic medication. Mean length of illness was 13.39 years, SD 10.91. In addition, the schizophrenia group contained a high proportion of individuals with a relatively severe history and/or a familial risk for psychosis.

The control group consisted of 102 females and 148 males, with a mean age of 36.8 years (s.d. $\pm$ 12.8 years). The control group was composed of volunteers from the general public, hospital nursing and medical staff, and university staff and students. Formal screening for schizophrenia or other psychological disorders was not undertaken in the control population. As such, the controls represent an unselected control group. To minimise population stratification bias, both control and clinical subjects were recruited in the Brisbane region (a city of approximately 2 million inhabitants on the East Coast of Australia) and all were of British or European descent.

Ethics approval was obtained from all institutions involved.

Selection of SNPs

Using the International HapMap Project (HapMap) phase II (Frazer *et al.*, 2007), seven tag-SNPs in *DRD2* with a minor allele frequency of 0.15 were selected. Tag-SNPs were identified using the pair-wise option of Tagger with a threshold of $r^2 > 0.8$.

Genotyping

Oragene kits were used to extract DNA from saliva samples. Samples were genotyped using a homogeneous MassEXTEND (hME) Sequenom assay performed by the Australian Genome Research Facility. The hME assay is based on the annealing of an oligonucleotide primer (hME primer) adjacent to the SNP of interest. The addition of a DNA polymerase along with a mixture of terminator nucleotides allows extension of the hME primer through the polymorphic site and generates allele-specific extension products, each having a unique molecular mass. The resultant masses of the extension products are then analysed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and

a genotype is assigned in real time. The hME assay was performed in multiplex with up to 36 reactions in a single well.

The genotyping fail rate was 4% for rs1752947; 6% for rs1760161; 4% for rs1800499; 5% for rs2734839; 3% for rs4245147; 3% for rs6275 and 4% for rs7131056. The genotyping of several other SNPs including *DRD2* rs6277 were independently verified by other methods such as real-time PCR with a concordance rate of 96.6 %. Genotypes were determined by investigators blinded for clinical diagnoses.

Statistical Analysis

A Pearson's chi-squared test was performed to identify statistical associations between alleles/genotype and schizophrenia status. Odds ratios (OR) were also calculated. Tests were performed on both genotype and allele data. Statistical tests were performed using the COMPARE2 program from the WinPepi suite of epidemiology programs (Abramson, 2004) and SPSS version 16.0. Hardy-Weinberg equilibrium (HWE) was computed using Utility Programs for Analysis of Genetic Linkage (Ott, 1988). The analysis of genotypes under a recessive model involved pooling the low-risk homozygotes and the heterozygotes and comparing frequencies with the high-risk homozygotes, i.e. OR > 1. Correction for multiple testing was conducted using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995). Linkage disequilibrium was calculated using JLIN version 1.6.0 (Carter *et al.*, 2006)

Results

A comprehensive genotype analysis of *DRD2* and its association with schizophrenia was undertaken using a haplotype block-based gene-tagging approach. A total of seven tag-SNPs that span from the 3'-end to the 5'-end of the gene were genotyped in a sample of 157

schizophrenia patients and 250 controls. One SNP was found to be significantly ($p = 0.0064$) associated with schizophrenia at the allele (Table 1). Rs2734839 was also significant at the genotype level (Table 2). Rs2734839 survived correction for multiple testing (corrected α-value was 0.012)

In the control and schizophrenia samples strong linkage disequilibrium (LD) was observed between rs2734839 and the previously reported rs6277 SNP (D' = 1 in the schizophrenia population; D' = 0.98 in the control population).

Genotype frequencies indicated that all polymorphisms were in HWE in both cases and control samples (rs2734839 controls $\chi^2 = 1.63$ $p = 0.20$ schizophrenia $\chi^2 = 0.066$ $p = 0.80$)

Examination of the genotype odds ratios (OR) of the rs2734839 SNP suggests a recessive pattern of inheritance. The heterozygous OR and the OR for the low-risk homozygote are approximately one (Table 2). Subsequently rs2734839 was found to be associated with schizophrenia when analysed under a recessive model by pooling genotypes ($p = 0.010$).

In order to evaluate whether there was any sexual dimorphism in the population, the male schizophrenia patients were analysed separately from the female patients. At the genotype level rs2734839 showed association with disease with a slightly weaker p-value (Pearson $\chi^2 = 7.375$ $p = 0.025$) for the males. The male schizophrenia samples remained in HWE. The remaining female cases were too small in number to analyse meaningfully.

A number of clinical parameters were also examined for association with *DRD2* variation. These included onset age, number of hospital admissions, family history, PANSS subscales, PANSS total, BARN subscales, BARN total, AIMS subscales, AIMS total, GHQ subscales, GHQ total and TMTA. A significant association was found for onset age and rs2734839. No other associations were observed. Analysis of variance revealed significant differences in

onset age between genotypes ($p = 0.011$, $F = 4.614$). Patients with the GG and GA genotypes had a mean onset age of 24.03 (95% C I= 20.87-27.19) and 24.25 (95% CI = 22.68-25.81) years whereas patients carrying the AA genotype had a mean onset age of 20.11 years (95% CI = 18.14-22.07). Post-hoc pairwise comparisons including Tukey and Bonferroni were undertaken to test differences between groups. Schizophrenia patients carrying the GA genotype had later schizophrenia onset age than those carrying the AA genotype (Tukey $P = 0.011$, Bonferroni $P = 0.012$).

For the six polymorphisms that did not show a significant association we did not have enough power (<0.80) to detect association with our sample size using retrospective power calculations for a case-control study in syntax SPSS version 18 because the odds ratios were so low(between 1.06 and 1.29). In fact a sample size ranging from 1000-19000 would be required to show any significance for these six polymorphisms with schizophrenia. It is most likely that the odds ratios are low because there is no biological role for these SNPs.

Discussion

Analysis of seven tag-SNPs in *DRD2* revealed associations with schizophrenia at the genotype and allele level for rs2734839 in an Australian schizophrenia cohort. Given the number of discordant gene association studies with schizophrenia it is likely to be a complex disorder with both environment and genetics playing a role. Although the genetic risk is high at 80% (McGuffin and Gottesman, 1999; Sullivan *et al.*, 2003) it is likely that no one gene accounts for this risk and a number of polymorphisms contribute. In a previous study we found an association with the rs6277 polymorphism and schizophrenia (Lawford *et al.*, 2005) and this association has been replicated by others (Betcheva *et al.*, 2009; Dubertret *et al.*, 2010; Fan *et al.*, 2010; Hanninen *et al.*, 2006; Hoenicka *et al.*, 2006; Monakhov *et al.*, 2008). The positive association with rs2734839 that we observed in this study appears novel. Interestingly, rs2734839 is in nearly complete LD with rs6277. Although rs6277 does not result in a non-synonymous polymorphism it does appear to have functional consequences on the protein translated (Duan *et al.*, 2003; Hirvonen *et al.*, 2005). There is still the possibility that rs2734839 is a functional SNP as other intronic SNPs in *DRD2* have been shown to have functional effects. The rs2283265 SNP and rs1076560 which are both intronic affect the D2 receptor long isoform and D2 receptor short isoform ratio of splice variants (Zhang *et al.*, 2007). The same SNPs were found to modulate working memory and attention (Zhang *et al.*, 2007). Therefore, the association we found between rs2734839 and schizophrenia first needs to be replicated in another sample set and secondly tested for functional effects.

Our results are similar to the findings of Dubertret et al. (Dubertret *et al.*, 2010) who identified a SNP (rs2242592) in the intergenic region of *DRD2* that is in strong LD with rs6277. As they observed a stronger association with rs2242592 than with rs6277, they concluded that an unknown functional SNP in LD with rs2242592 is likely to be identified in the future. It is possible that a functional SNP exists in non-coding region and has been

overlooked by focus on protein coding regions. Evidence is now showing that non-coding RNAs are also regulators of human disease (Taft *et al.*, 2010).

Like Fan et al. (Fan *et al.*, 2010) we did not find an association with rs6275 and schizophrenia. It is likely that there is no biological role for this SNP in schizophrenia as there was no indication of a bias toward schizophrenia (OR = 1.18). Contrary to our observations, this polymorphism was shown previously to be associated with schizophrenia and the same study found it interacts with rs4680 in COMT to increase schizophrenia susceptibility (Gupta *et al.*, 2009). Earlier studies in an Indian and Russian population also found an association with schizophrenia (Kukreti *et al.*, 2006; Monakhov *et al.*, 2008), however both studies observed departure from HWE in the case population.

The rs2734839 polymorphism was also found to be significantly associated with later onset age. In patients carrying the associated allele (G) onset age was delayed by an average of 4 years. The average onset age for the AA genotype was only 20 years suggesting that this polymorphism is associated with a youth onset subset of schizophrenia. Other studies have also observed polymorphisms to be associated with onset age in schizophrenia. One of these studies suggested that a polymorphism in the *CCR5* gene is a susceptibility factor for schizophrenia with late onset or alternatively the polymorphism may act as a modifier by delaying the onset of schizophrenia without affecting disease susceptibility (Rasmussen *et al.*, 2006). Our study is different from this one in that they did not find a significant association between the *CCR5* polymorphism and schizophrenia, only onset age. Therefore in our study it is likely that the rs2734839 polymorphism is associated with schizophrenia but only in a subset of patients with delayed onset. For the early onset group (mean age 20) other genes are likely to be responsible.

Our significant association between the rs2734839 polymorphism and schizophrenia needs to be replicated in a larger sample size and other defined ethnic groups. Our study does not rule out population stratification but the affects are likely to be small as patients and controls were all Caucasians from Australia. The significant association seen with rs2734839 and schizophrenia onset age must be seen as exploratory until it is tested in a larger sample set of equal numbers of cases and controls. Unfortunately we did not have access to a defined group of late onset patients (onset age over 40 years). Our patient group was mainly early onset with 23 years the average age of first diagnosis. Ideally this study would need to be repeated with a defined set of early and late onset patients.

Conclusions

We have found a significant association between schizophrenia and a polymorphism rs2734839 in the *DRD2* gene. This same polymorphism was also shown to be associated with schizophrenia onset age. The *DRD2* region has shown consistent evidence for association with schizophrenia and it is likely that many genetic variants interact together modulating dopamine signalling.

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Author Disclosure Statement

The authors state that no competing financial interests exist.

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Table 1

Allele association of 7 *DRD2* SNPs with schizophrenia

SNP ID	Allele frequency		Position*	SNP details	χ^2	*p*-value†	Odds Ratio	95% CI
rs17529477	A	G						
control	152	318	112822277	Intron 1	2.139	0.144	1.27	0.91-1.76
SZ	85	225						
rs17601612	C	G						
control	187	269	112822955	Intron 1	2.740	0.098	1.29	0.94-1.76
SZ	108	200						
rs4245147	C	T						
control	239	245	112823217	Intron 1	1.162	0.281	1.17	0.87-1.58
SZ	140	168						
rs7131056	A	C						
control	194	276	112834984	Intron 1	0.131	0.718	1.06	0.78-1.43
SZ	132	178						
rs1800499	A	G						
control	16	448	112792904	Exon 2	0.085	0.771	1.12	0.48-2.56
SZ	12	300						
rs2734839	A	G						
control	288	180	112791700	Intron 3	7.433	0.0064	1.50	1.11-2.03
SZ	158	148						
rs6275	C	T						
control	335	143	112788687	Exon 5	1.083	0.298	1.18	0.85-1.62
SZ	205	103						

***** Nucleotide position on the chromosome 11 reference sequence

† *p*-value determined by Pearson's chi-squared test

Table 2

Genotype association of rs2734839 with schizophrenia.

Polymorphism	**Genotype counts (%)**			***p*-value***
rs2734839	AA	GA	GG	
Control	84 (35.9)	120 (51.3)	30 (12.8)	0.016
schizophrenia	40 (26.1)	78 (51.0)	35 (22.9)	0.005†
Odds Ratio‡	1	1.37	2.45	
(*p*-value)		(0.388)	(0.008)	

* *p*-value determined by Pearson's χ^2 test

† *p*-value determined using the extended Mantel-Haenszel test for trend

‡ OR, with respect to the genotype that was not associated with schizophrenia