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Dysbindin (*DTNBP1*) variants are associated with hallucinations in schizophrenia

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Running title: *DTNBP1* associated with hallucinations in schizophrenia

Abstract

Background: Dystrobrevin binding protein 1 *DTNBP1* is a schizophrenia susceptibility gene involved with neurotransmission regulation (especially dopamine and glutamate) and neurodevelopment. The gene is known to be associated with cognitive deficit phenotypes within schizophrenia. In our previous studies, *DTNBP1* was found associated not only with schizophrenia but with other psychiatric disorders including psychotic depression, post-traumatic stress disorder, nicotine dependence and opiate dependence. These findings suggest that *DNTBP1* may be involved in pathways that lead to multiple psychiatric phenotypes. In this study we explored the association between *DTNBP1* SNPs (single nucleotide polymorphisms) and multiple psychiatric phenotypes included in the Diagnostic Interview of Psychosis (DIP).

Methods: Five *DTNBP1* SNPs, rs17470454, rs1997679, rs4236167, rs9370822 and rs9370823 were genotyped in 235 schizophrenia subjects screened for various phenotypes in the domains of depression, mania, hallucinations, delusions, subjective thought disorder, behaviour and affect, and speech disorder. SNP-phenotype association was determined with ANOVA under general, dominant/recessive and over-dominance models.

Results: Post-hoc tests determined that SNP rs1997679 was associated with visual hallucination; SNP rs4236167 was associated with general auditory hallucination as well as specific features including non-verbal, abusive and third-person form auditory hallucinations; and SNP rs9370822 was associated with visual and olfactory hallucinations. SNPs that survived correction for multiple testing were rs4236167 for third-person and abusive form auditory hallucinations; and rs9370822 for olfactory hallucinations.

Conclusion: These data suggest that *DTNBP1* is likely to play a role in development of auditory related, visual and olfactory hallucinations which is consistent with evidence of

DTNBP1 activity in the auditory processing regions, in visual processing and in the regulation of glutamate and dopamine activity.

1.   Introduction

Schizophrenia is a highly heritable psychiatric disorder affecting approximately 1% of the population worldwide [1]. It has devastating consequences for those affected and their families and amounts to $19 billion of financial burden per annum in the USA [2]. Treatments targeting symptoms are only partially successful and there is limited understanding of schizophrenia aetiology. Progress in the understanding of the molecular aetiology of schizophrenia has been slow owing to the complex nature of the disorder and the heterogeneity of schizophrenia phenotypes. Early efforts focused on identifying schizophrenia susceptibility genes via case/control association studies. Results were often inconsistent or could not be replicated, perhaps because it is such a heterogeneous disorder. It is possible that clinically distinct forms of schizophrenia are the result of discrete combinations of susceptibility genes. Hence, this study is aimed at identifying the role that susceptibility genes play in specific clinical symptoms within schizophrenia rather than concentrating on the diagnosis of schizophrenia.

Dystrobrevin binding protein 1 (*DTNBP1*) is a gene implicated in schizophrenia susceptibility. It encodes a protein that binds to alpha- and beta-dystrobrevin in muscle and brain [3]. Association studies have identified several *DTNBP1* SNPs and haplotypes associated with negative symptoms of schizophrenia including poverty of speech, emotion, motivation and social interaction [4,5]. *DTNBP1* mRNA expression is also reduced in the cortex and hippocampus of schizophrenia patients [6-8], suggesting that *DTNBP1* plays a role in the aetiology of this disease perhaps by affecting brain development. Imaging studies have identified that *DTNBP1* polymorphisms are associated with grey and white matter volume loss [9]. In rodents, *DTNBP1* is highly expressed during embryonic stages [10,11] and

reduced *DTNBP1* expression in cultured neurons leads to abnormal neuronal growth and dendritic morphology [10-13]. *DTNBP1* has also been shown to play a role in neurotransmission by modulating the expression of two cell-surface receptor classes; the N-methyl-D-aspartate receptor (NMDAR) [14] and the dopamine D2 receptor (DRD2) [15,16]. These findings suggest that *DTNBP1* may play a role in the pathogenesis of schizophrenia by altering both brain development and neurotransmission activity.

We have previously identified association of *DTNBP1* SNPs with schizophrenia as well as several other psychiatric phenotypes [17-19]. These SNPs include one non-synonymous SNP rs17470454 (causing a proline to serine substitution) and four intronic SNPs rs1997679, rs4236167, rs9370822 and rs9370823. We found association between rs1997679, rs4236167, rs9370822, rs9370823 and schizophrenia in an Australian schizophrenia cohort ($n = 160$) [18] and the same SNPs were found associated with psychotic depression in a major depressive disorder cohort ($n = 243$) [17]. Interestingly, as well as schizophrenia, the *DTNBP1* SNP rs9370822 was found associated with several other disorders including post-traumatic stress disorder (PTSD), nicotine dependence and opiate dependence but not alcohol dependence [19].

The objective of this study was to further explore the association between various psychiatric phenotypes in schizophrenia and *DTNBP1* SNPs which have been found previously associated with schizophrenia or other psychiatric disorders.

2.   Methods

2.1.   Subjects

2.1.1   Schizophrenia patients

The participants consist of 235 schizophrenia patients of European descent with a mean age of 43.9 years (s.d $\pm$ 10.7 years). There were 70 females and 165 males with a confirmed diagnosis of schizophrenia according to DSM-IV/ICD-10 diagnostic criteria with a mean onset age of 23.18 years (s.d $\pm$ 6.31 years). All participants underwent a clinical and neuropsychological assessment and provided a blood sample at the time of assessment. The participants were assessed using a clinical assessment battery that consists of the Diagnostic Interview for Psychosis (DIP) [20] to collect clinical measures including depression, mania, hallucinations, subjective thought disorder, delusions, behaviour and affect, and speech disorder (Figure 1; details in Supplementary Table 1). The patients were recruited from several sources across five Australian States and Territories (New South Wales, Australian Capital Territory, Queensland, Western Australia and Victoria) using media advertisements, inpatient, outpatient and community mental health service providers, non-government organisations and rehabilitation services.

2.1.2   Controls

The control group was also obtained from the Australian Schizophrenia Research Bank. The controls consisted of 121 females and 104 males of European descent, with a mean age of 45.00 years (s.d. $\pm$ 13.2 years). Healthy controls were screened for a family history of, or treatment for, a psychiatric illness at the time of registration. The controls underwent a clinical and neuropsychological assessment and provided a blood sample at the time of assessment. The controls were assessed using a clinical assessment battery that consists of

the Diagnostic Interview for Psychosis (DIP) [20] to collect socio-demographic, family and medical history data.

2.1.3 Ethics

Each participant gave written informed consent before commencement of data collection. Ethics approval for the project was obtained from the Human Research Ethics Committee of the Queensland University of Technology. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. SNP Genotyping

Samples were genotyped for the *DTNBP1* SNPs rs17470454, rs1997679, rs4236167, rs9370822 and rs9370823 essentially as previously described [18], using a homogeneous MassEXTEND (hME) Sequenom assay performed by the Australian Genome Research Facility.

2.3. Statistical Analysis

Clinical measures were analysed by ANOVA (analysis of variance) using Statistical Package for the Social Sciences (SPSS) 21 to detect score differences between genotypes under linear and quadratic models in schizophrenia patients. Clinical measure scores range from 0-2. A higher score means a higher clinical severity for a clinical measure. SNPs associated with general auditory hallucinations were further analysed for association with other forms (specific features) of auditory hallucinations. The genotypes were analysed under general, dominant/recessive and over-dominant models. Hardy-Weinberg equilibrium was tested using Utility Programs for Analysis of Genetic Linkage [21]. Correction for multiple testing was conducted using the Benjamini-Hochberg method [22].

3.   Results

DTNBP1 SNPs rs17470454, rs1997679, rs4236167,rs9370822 and rs9370823 were tested for association with schizophrenia followed by all clinical measures covered in the depression, mania, hallucinations, subjective thought disorder, delusions, behaviour and affect, and speech disorder domains (Supplementary table 1). All genotypes were found to be in Hardy-Weinberg equilibrium ($P > 0.05$). All five SNPs were not associated with schizophrenia after comparing genotype frequencies of the five SNPs between schizophrenia patients and healthy controls. Clinical measure analysis revealed that the only domain to show consistent association was the hallucination domain. Multiple clinical measures within the hallucination domain were associated with *DTNBP1* SNPs (Table 1).

Retrospective power calculations determined that there was sufficient power (80%) to detect at least one hallucination phenotype for each SNP. There was insufficient power to detect association with some hallucination phenotypes (as low as 1.78%, requiring a sample size up to 74622). No significant differences were detected between gender and hallucination measure scores. Risk genotypes for each SNP were determined using mean scores and post-hoc pairwise comparisons between genotypes for the associated psychiatric measures (Figures 2-4).

SNP rs17470454 was found associated with only one hallucination measure (olfactory hallucination) with a best-fit linear model. However, rs17470454 has a very low minor allele frequency and there was only one AA genotype count in our sample, hence rs17470454 was excluded from post-hoc analysis.

SNP rs1997679 was associated with visual hallucination with a best-fit quadratic model (Figure 2). Individuals with CC and CT genotypes had higher scores for visual hallucination compared to those with the TT genotype. Post-hoc Tukey's test was also significant for CT versus TT genotypes ($P = 0.023$), suggesting that the C allele is inherited dominantly ($P = 0.025$ when analysed as a C-dominant trait).

SNP rs4236167 was associated with visual hallucination with a best-fit quadratic model and general auditory hallucination with neither best-fit model (Figure 3a). Further analysis of specific features of auditory hallucination (Table 2) also revealed SNP association with non-verbal form auditory hallucination with best-fit linear and quadratic models, abusive form auditory hallucination with best-fit linear and quadratic models, and third-person form auditory hallucination with best-fit linear model (Figure 3b). For all auditory related hallucination measures, individuals with CC and CT genotypes had higher mean scores than those with the TT genotype. Post-hoc Tukey's test was significant for general auditory hallucination ($P = 0.040$ for CT versus TT), non-verbal ($P = 0.009$ for CT versus TT), abusive ($P = 0.003$ for CT versus TT) and third-person form ($P = 0.004$ for CC versus TT; 0.001 for CT versus TT) auditory hallucinations. These results suggest the C allele is likely a dominant allele for the auditory related hallucination phenotypes ($P = 0.017$ for general auditory hallucination, $P = 0.003$ for non-verbal form, $P = 0.002$ for abusive form and $P = 0.0001$ for third-person form auditory hallucinations, when analysed as a C-dominant trait). For visual hallucination measure, heterozygote individuals had higher mean score than those who are homozygotes for both C and T allele. Post-hoc Tukey's test was significant for CT

versus TT genotypes (P = 0.026). Visual hallucination mean scores and further analysis under a dominant model for rs4236167 (P = 0.004) suggests a dominant mode of inheritance.

SNP rs9370822 was associated with visual hallucination with a best-fit quadratic model and olfactory hallucination with a best-fit quadratic model (Figure 4). Individuals with AA and AC genotypes had higher olfactory and visual hallucination scores than the CC genotype. Tukey's test was significant between AC and CC genotypes for visual hallucination ($P = 0.025$) and olfactory hallucination ($P = 0.030$), suggesting that the A allele is inherited dominantly for these clinical measures ($P = 0.042$ for visual hallucination, $P = 0.006$ for olfactory hallucination) under an A-dominant model.

Associations that survived multiple testing correction were rs4236167 with third-person form auditory hallucination ($P = 0.001$, $q = 0.010$), rs4236167 with abusive form auditory hallucination ($P = 0.005$, $q = 0.010$), and rs9370822 with olfactory hallucination ($P = 0.004$, $q = 0.0125$).

4.   Discussion

Following earlier findings of association between *DTNBP1* SNPs and various cognitive phenotypes in schizophrenia [4-8,18,19,23-25], the current study explored the relationship between *DTNBP1* SNPs and schizophrenia phenotypes. We found that rs1997679, rs4236167 and rs9370822 were associated with various phenotypes within the hallucinations domain in an Australian schizophrenia cohort, especially for auditory related hallucinations. However, the functional role of rs1997679, rs4236167 and rs9370822 is still unclear. If any

of these SNPs are functional, it is likely that they are altering *DTNBP1* expression by affecting gene splicing or transcription as they are all located intronically. Alternatively, they may simply be in disequilibrium with other functional *DTNBP1* SNPs.

One of the key features of schizophrenia is hallucinations. The dopamine and glutamate systems have been implicated in the development of hallucinations as drugs with strong dopaminergic effect and glutamate antagonists are known to induce hallucinations [26]. *DTNBP1* has been reported to be involved in impaired visual processing function and reduced occipital lobe volume in schizophrenia patients [27,28]. The role of *DTNBP1* in visual processing, along with its role in glutamate and dopamine neurotransmission suggests that *DTNBP1* plays a key role in the pathogenesis and development of hallucinations.

To our knowledge, no extant study has reported the association of *DTNBP1* SNPs with hallucination phenotypes. Previous association studies emphasised the relationship between *DTNBP1* SNPs and cognitive related phenotypes including executive function deficits, processing speed reduction and working memory deficits [4,5,23]. Association studies are also supported by reports that schizophrenia individuals with poorer cognitive performance have reduced *DTNBP1* levels in the prefrontal cortex and hippocampal formation pertaining executive and working memory functions [6-8,24,25]. Mouse studies have also demonstrated that heterozygous and homozygous *DTNBP1* knockout mice display schizophrenia-like cognitive deficits. As well as reduced *DTNBP1* mRNA levels, knockout mice have decreased glutamate release and decreased glutamate receptor function in the hippocampal and prefrontal regions [29-31].

It has been demonstrated that PCP (phencyclidine) exhibits antagonistic effects on NMDARs and use of PCP causes schizophrenia-like symptoms including positive symptoms, negative symptoms, and cognitive deficits [32]. Therefore, the glutamate system is believed to mediate multiple psychophysiological processes not limited to cognitive processes. Subsequent pharmacological models linking glutamate system hypofunctioning and schizophrenia-like symptoms (which include cognitive deficits as well as hallucinations) have been developed [33,34]. Considering *DTNBP1* has a functional role in glutamate release [31,35], it is possible that *DTNBP1* may also play a role in the pathogenesis of multiple psychiatric phenotypes including hallucinations (as found in the present study).

SNP rs17470454 is a non-synonymous SNP causing a Pro191Ser substitution. One study reported marginal association between rs17470454 and bipolar disorder at the allele level [36]. The present study detected a dominant association between the A allele and olfactory hallucination. However, there is no evidence in the literature that could explain the biological significance of rs17470454 found associated to the identified hallucination phenotypes.

It is known that levels of *DTNBP1* mRNA are lower in various brain regions in schizophrenia, including the hippocampus and the superior temporal gyrus (STG) [6,8]. The hippocampus is involved in working memory [37] as hippocampus volume reduction has been significantly correlated with the degree of executive function and memory deficits [38-41]. The STG plays a role in processing auditory information as it consists of the primary auditory cortex, auditory belt and the auditory parabelt [42-44]. Reduction in STG volume

has been found associated with the severity of auditory hallucinations [45-48]. It is possible that rs1997679, rs4236167 and rs9370822 play a role in the pathogenesis of auditory hallucinations due to their influence on *DTNBP1* expression in brain regions affected in schizophrenia. *DTNBP1* may be implicated in visual hallucinations as *DTNBP1* risk haplotype has been reported in schizophrenia patients with impaired visual processing and reduced occipital lobe volume [27,28]. The abundant expression of glutamate and dopamine receptors in the olfactory epithelium [49] also suggests that *DTNBP1* may have a role in olfactory hallucination due to the influence of *DTNBP1* on glutamate and dopamine activity.

The SNPs investigated in the present study differed from *DTNBP1* SNPs found associated with cognitive deficits in many previous studies [23,50-58] (including intronic variants rs2619539, rs3213207, rs1011313, rs2619528, rs760761, rs2619522, rs1018381, and rs909706). The three associated SNPs in the present study are also intronic (rs1997679 located ~4kb downstream of exon 1; rs4236167 located ~320bp upstream of 3' –ag intron end; rs9370822 located ~11kb upstream of exon 8) but not in close proximity to the "gt-" nor "-ag" splicing consensus. The three SNPs are situated within clusters of DNase hypersensitive sites according to the ENCODE genome browser (http://genome.ucsc.edu/ENCODE/). According to HapMap, SNPs rs1997679 and rs9370822, but not rs4236167, are in linkage disequilibrium with a functional SNP (rs1047631) where the A allele was reported to reduce *DTNBP1* mRNA [59]. This suggests a possibility that the association found with rs1997679 and rs9370822 may be due to strong linkage disequilibrium with the functional SNP rs1047631. SNP rs4236167 however, may be in linkage disequilibrium with another unknown functional SNP, or may be functional itself due to its location within a DNase hypersensitive site which may influence the transcriptional activity of a gene.

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The finding of association between *DTNBP1* SNPs and auditory hallucinations suggests that hypofunction of *DTNBP1* in brain regions that process auditory information may be responsible for the development of auditory hallucinations. Unlike the association between *DTNBP1* and cognitive impairment, there is lack of direct evidence in the literature to support the association between *DTNBP1* and hallucinations. A plausible alternative explanation for our findings is that hallucinations may be a secondary phenotype caused by visual as well as cognitive impairment. One study found that auditory and visual hallucinations were associated with lower cognitive baseline and rapid cognitive decline in Alzheimer's disease [60]. The positive association between the *DTNBP1* SNPs and hallucinations found in the present study may be due to the presence of visual and cognitive impairment which may be the primary cause of hallucinations, especially visual and auditory hallucinations.

In addition to the association of *DTNBP1* variants with cognitive deficits, we conclude that rs1997679 is associated with visual and auditory related hallucinations; rs4236167 is associated with auditory related hallucinations; and rs9370822 is associated with visual, olfactory and auditory related hallucinations.

Funding Statement

Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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Tables

Table 1: Genotype association of five *DTNBP1* SNPs with various clinical measures of schizophrenia.

SNP	Genotypes	Hallucination measure mean scores[a]		
		Visual	Olfactory	Auditory
rs17470454	AA	2.00 (1)	2.00 (1)	2.00 (1)
	AG	0.82 (22)	0.59 (22)	1.50 (22)
	GG	0.85 (168)	0.25 (167)	1.36 (168)
		$P = 0.409$	***P = 0.001***	$P = 0.557$
rs1997679	CC	0.80 (99)	0.30 (99)	1.34 (99)
	CT	1.01 (78)	0.28 (78)	1.49 (78)
	TT	0.36 (14)	0.31 (13)	1.00 (14)
		P = 0.021	$P = 0.971$	$P = 0.102$
rs4236167	CC	0.71 (49)	0.17 (48)	1.41 (49)
	CT	1.04 (89)	0.37 (89)	1.49 (83)
	TT	0.66 (53)	0.28 (53)	1.15 (53)
		P = 0.015	$P = 0.160$	***P = 0.050***
rs9370822	AA	0.77 (71)	0.26 (70)	1.45 (71)
	AC	1.04 (83)	0.43 (83)	1.41 (83)
	CC	0.59 (37)	0.05 (37)	1.16 (37)
		P = 0.021	***P = 0.004***	$P = 0.196$
rs9370823	AA	0.81 (100)	0.29 (99)	1.39 (100)
	AG	1.01 (70)	0.36 (70)	1.41 (70)
	GG	0.52 (21)	0.10 (21)	1.19 (21)
		$P = 0.056$	$P = 0.213$	$P = 0.534$

[a]score ranges from 0-2

Table 2: Genotype association of rs4236167 with specific features of auditory hallucinations.

| Genotypes | Specific features of auditory hallucination mean scores | | | |
	Nonverbal	Abusive	Commentary	Thirdperson
CC	0.70 (47)	1.13 (53)	0.58 (53)	0.81 (53)
CT	0.80 (89)	1.27 (101)	0.50 (101)	0.79 (101)
TT	0.36 (53)	0.78 (55)	0.44 (55)	0.29 (55)
	$P = 0.011$	$P = 0.005$	$P = 0.640$	$P = 0.001$

Figure Legends

Figure 1: DIP clinical measures used for assessment of schizophrenia patients.

Figure 2: Mean hallucination scores for *DTNBP1* rs1997679 genotypes.
* indicates post-hoc Tukey's $P < 0.05$ compared with the genotype with lowest score. Error bars indicate ±SD.

Figure 3a: Mean hallucination scores for *DTNBP1* rs4236167 genotypes.
* indicates post-hoc Tukey's $P < 0.05$ compared with the genotype with lowest score, ** indicates post-hoc Tukey's $P < 0.01$ compared with the genotype with lowest score. Error bars indicate ±SD.

Figure 3b: Mean hallucination specific feature scores for DTNBP1 rs4236167 genotypes.
** indicates post-hoc Tukey's $P < 0.01$ compared with the genotype with lowest score. Error bars indicate ±SD.

Figure 4: Mean hallucination scores for *DTNBP1* rs9370822 genotypes.
* indicates post-hoc Tukey's $P < 0.05$ compared with the genotype with lowest score. Error bars indicate ±SD.