Bipolar Disorder and Polymorphisms in the Dysbindin Gene (*DTNBP1*)

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Background: *Several studies support the dysbindin (dystrobrevin binding protein 1) gene (DTNBP1) as a susceptibility gene for schizophrenia. We previously reported that variation at a specific 3-locus haplotype influences susceptibility to schizophrenia in a large United Kingdom (UK) Caucasian case-control sample.*

Methods: *Using similar methodology to our schizophrenia study, we have investigated this same 3-locus haplotype in a large, well-characterized bipolar sample (726 Caucasian UK DSM-IV bipolar I patients; 1407 ethnically matched controls).*

Results: *No significant differences were found in the distribution of the 3-locus haplotype in the full sample. Within the subset of bipolar I cases with predominantly psychotic episodes of mood disturbance* (n = *133) we found nominally significant support for association at this haploptype* ($p < .042$) *and at SNP rs2619538* ($p = .003$), *with a pattern of findings similar to that in our schizophrenia sample. This finding was not significant after correction for multiple testing.*

Conclusions: *Our data suggest that variation at the polymorphisms examined does not make a major contribution to susceptibility to bipolar disorder in general. They are consistent with the possibility that DTNBP1 influences susceptibility to a subset of bipolar disorder cases with psychosis. However, our subset sample is small and the hypothesis requires testing in independent, adequately powered samples.*

Key Words: Dysbindin, *DTNBP1*, bipolar disorder, schizophrenia, association

Family, twin and adoption studies provide evidence that genetic factors are important in determining susceptibility to bipolar disorder and that there is a range in phenotypic expression of this genetic predisposition (Craddock and Jones 1999). While single genes may play a major role in a small minority of families, the inheritance of most bipolar disorder is consistent with the action of both multiple genes of small to moderate effect and environmental factors (Craddock et al 1995).

Traditionally psychiatric research in general, and the search for predisposing genes in particular, has proceeded under the assumption that schizophrenia and bipolar disorder are separate disease entities with separate underlying etiologies (and treatments) - the so-called "Kraepelinian dichotomy" (Kraepelin 1919). However, several findings from genetic research suggests that there is not a neat biological distinction between schizophrenia and bipolar disorder. First, although family studies have demonstrated that to a first approximation, schizophrenia and bipolar disorder "breed true" (Gershon et al 1982; Maier et al 1993), families are known in which there are multiple cases of schizophrenia, bipolar disorder and cases with both psychosis and mood disorder occur (eg. Pope and Yurgelun-Todd 1990) and systematic family studies point to the existence of a non-trivial degree of familial co-aggregation between schizophrenia and bipolar illness (eg. Valles et al 2000). Second, a graphic illustration of the varied expression of the same set of susceptibility genes is provided by the Maudsley triplets—a set of identical triplets, two of whom had a Research Diagnostic Criteria (RDC; Spitzer et al 1978) lifetime diagnosis of schizophrenia and the third an RDC lifetime diagnosis of bipolar I Disorder (McGuffin et al 1982). Third, a recent twin study that used an analysis unconstrained by the diagnostic hierarchy inherent in current classification systems (ie. the principle that schizophrenia "trumps" mood disorder in diagnosis) demonstrated an overlap in the genetic susceptibility to mania and schizophrenia (Cardno et al 2002). Fourth, genetic linkage studies have demonstrated some chromosome regions that show convergent or overlapping regions of interest in both disorders – including regions of 13q, 22q and 18 (Badner and Gershon 2002; Berrettini 2003). Fifth, recent reports implicating variation at the G72/G30 locus on chromosome 13q in both schizophrenia (Chumakov et al 2002; Schumacher et al 2004) and bipolar disorder (Hattori et al 2003; Chen et al 2004; Schumacher et al 2004) suggest that the substantial circumstantial and genetic evidence is starting to find molecular genetic support.

Given this background, it is important that any gene found to influence susceptibility to schizophrenia should also be examined in bipolar disorder. Here we report our findings in bipolar disorder with polymorphisms in the *dysbindin* (*dystrobrevin binding protein 1*) gene (*DTNBP1*), a gene implicated in the pathogenesis of schizophrenia by studies from several groups.

DTNBP1 encodes dysbindin-1, is ubiquitously expressed and is located on 6p22.3, one of the best-supported regions that have emerged from linkage studies of schizophrenia (Straub et al 1995, 2002a; Moises et al 1995; Maziade et al 1997; Schwab et al 2000). Straub and colleagues (Straub et al 2002b) undertook linkage disequilibrium studies across this region in 270 multiply affected Irish pedigrees that showed linkage in this region and demonstrated significant association between schizophrenia and several individual SNPs and marker haplotypes across the *DTNBP1* gene. Subsequently association at this gene, albeit with different haplotypes, was replicated in a parent-offspring trios sample of German, Hungarian and Israeli origin (Schwab et al 2003) and in parent-offspring trios of Bulgarian origin (Kirov et al 2004) but

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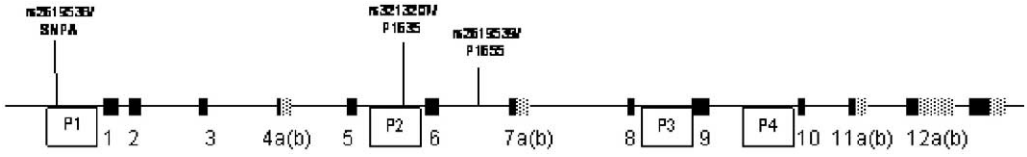

Figure 1. Exon structure of DTNBP1, showing exons for the predicted transcripts from AceView (http://ncbi.nlm.gov/IEB/Research/Acembly/index.html?human) as previously described by Williams et al (2004). The relative locations of the single nucleotide polymorphisms genotyped P1655, P1635, and SNPA, are shown. The shaded areas of exons 4, 7, 11, 12, and 13 represent alternative splicing. P1, P2, P3 and P4 represent the proposed location of the promoters 1, 2, 3, and 4 respectively.

not in a case control study of Caucasian Irish individuals (Morris et al 2003). Recently, our group undertook a detailed study of the dysbindin gene in 708 schizophrenia cases and 711 controls of Caucasian UK subjects. The gene was screened in schizophrenic individuals, new variants were identified and a total of 20 polymorphisms were examined. Strong evidence for association ($p < .0006$) with multiple novel 3-marker haplotypes was seen. We were able to replicate this finding (Williams et al 2004) within the case-control sample originally reported by Morris et al (2003) as being negative with the polymorphisms originally typed by that group.

In the current study we have examined this same 3 locus haplotype (P1655 (rs2619539), P1635 (rs3213207), and SNP A (rs2619538); see Figure 1) in our bipolar I case-control sample of Caucasian UK origin (BPI: $n = 726$, controls: $n = 1407$) and find no evidence that variation at this haplotype influences risk to bipolar disorder in general but some evidence that it may influence susceptibility to illness in the subset of bipolar individuals in whom there is frequent occurrence of psychotic symptoms.

Methods and Materials

Subjects

All subjects in these studies were Caucasian and of UK origin and provided written informed consent to participate in genetic studies. Protocols and procedures were approved by relevant ethical review panels, including the UK West Midlands Multisite Regional Ethics Committee and the South Birmingham Local Research Ethics Committee.

Bipolar Probands

All the cases used met DSM-IV (American Psychiatric Association 1994) criteria for bipolar I disorder and were recruited through mental health services in England and Wales. Diagnoses were made by the consensus lifetime best estimate method (Leckman et al 1982) on the basis of all available information including a semi-structured interview and review of psychiatric case records. The patients were interviewed using Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al 1990) and psychiatric/general practice case-notes were reviewed. These data were combined for each participant to form a written case-vignette. Based on the information contained in the vignettes, best-estimate lifetime diagnoses were made according to DSM-IV (American Psychiatric Association 1994). The vignettes were also used to make consensus best-estimate ratings of key clinical variables relating to psychosis using the bipolar Affective Disorder Dimensional Scale (BADDS) (Craddock et al 2004). A score in the range 1–100 on the Psychosis (P) dimension shows the best estimate of the proportion of total episodes of illness in which psychotic features occurred. A score in the range 1 – 100 on the Incongruence (I) dimension shows the best estimate of the overall balance between mood congruent and mood-incongruent psychotic features according to definitions of mood congruence given in DSM-IV (American Psychiatric Association 1994) and the rating guidelines for BADDS (Craddock et al 2004). Within current classifications, one of the key features of schizophrenia is the presence of psychotic features, particularly those that are "mood-incongruent," that is, they are not understandable within the context of mood state (American Psychiatric Association 1994; World Health Organization 1993). We, therefore, hypothesized that the subset of bipolar patients who experienced psychotic features would be most likely to show evidence for an influence of susceptibility from *DTNBP1*. Because the optimal subset of psychotic bipolars to test this hypothesis is not known, we chose to examine 3 subsets: A) Bipolar cases with lifetime occurrence of at least one psychotic symptom (corresponding to a score on the BADDS Psychosis dimension of $P \geq 10$), B) Bipolar cases in which at least 50% of episodes of illness were accompanied by psychotic features (corresponding to a score on the BADDS Psychosis dimension of $P \geq 50$), and C) Bipolar cases with psychotic symptoms which were predominantly mood incongruent (corresponding to a score on the BADDS Incongruence dimension of $I \geq 20$). Other key clinical variables were rated according to written operational guidelines in use by our group and available on request from the authors. These included age at onset of impairment by illness, lifetime occurrence of rapid cycling, lifetime occurrence of postpartum triggering of episodes and family history of psychiatric illness. Team members involved in the interview, rating and diagnostic procedures were either a fully trained research psychologist or psychiatrist. Inter-rater reliability was high. This was formally assessed using 20 cases and resulted in mean kappa statistics of .85 for DSM-IV diagnosis. Mean kappa statistics for the key clinical variables ranged from .81–.99. Formative clinical team reliability meetings took place weekly. Demographic and key clinical features of the patient sample are shown in Table 1.

Control Individuals

Consent was obtained for control subjects following local ethical approval guidelines. Demographic features of the controls are shown in Table 1. Controls were all of Caucasian UK origin collected from two sources:

The British Blood Transfusion Service ($n = 1298$). The sample was not specifically screened for psychiatric illness but individuals were not taking regular prescribed medications. In the UK, blood donors are not remunerated even for expenses and are, therefore, not over-represented for indigents or for the socially disadvantaged.

Family Practitioner Clinic ($n = 109$). Individuals were recruited from amongst those attending for nonpsychiatric reasons. This sample was screened to exclude a personal history of mood disorder.

Table 1. Demographic and Clinical Features of Samples Used in the Current Study

Group	Feature	
Bipolar I Probands (n = 726)	% Males	38.2
	Mean (SD) age at interview	47.7 (13.1) years
	Mean (SD) age at onset	26.2 (10.1) years
	Family history of psychiatric illness in first or second degree relative	59.8%
	% Lifetime rapid cycling	12.4%
	% Lifetime occurrence of at least one psychotic symptom	63.4%
	% Psychotic symptoms occur in 50% or more of episodes of illness	18.3%
	% Predominantly mood incongruent psychotic features	21.6%
	% Lifetime occurrence of puerperal triggering of mood episodes	15.8%
Controls (n = 1407)	% Males	52.4
	Mean (SD) age at sampling	40.8 (12.5) years

Genotyping

Genotyping was performed within the Neuropsychiatric Genetics Laboratory in Cardiff using the Amplifluor™ method (Myakishev et al 2001) which is based upon allele-specific amplification and universal energy-transfer-labeled primers. The allele specific products were resolved on an Analyst AD fluorescence reader (LJL Biosystems, California).

Statistical Analysis

Departure from Hardy-Weinberg equilibrium was tested using a $\chi 2$ goodness-of-fit test. Tests for differences between allele and haplotype frequencies were performed using UNPHASED 2.40 (Dudbridge 2003). The effect of alleles/haplotypes was assumed to be additive. For the main and sub-phenotype analyses we tested for differences in the distributions of 3-locus haplotypes as the primary analysis. Further, in order to reduce degrees of freedom and thereby maximize power we undertook a test in which we considered only 3 classes of haplotype: "risk," "protective," and "other" (as observed in our previous schizophrenia analysis). Uncertain haplotypes were estimated using the EM algorithm within UNPHASED. Single locus allele and also genotype tests, allowing for dominance effects, were also performed. Nominally significant asymptotic p-values were confirmed by permuting the case/control status over 50,000 replicates and observing the maximum test statistic in each case.

Power Estimation. The power of our full sample to detect an effect of the magnitude of that previously observed in our schizophrenia sample (odds ratio of 1.3 conferred by risk haplotype and .70 for the protective haplotypes) was estimated using the Genetic Power Calculator (Purcell et al 2003) under the assumption of a multiplicative model. The power to detect this haplotype effect in the bipolar sample exceeded .99 (alpha = .001).

Results

The control individuals were genotyped in two waves, one typed with our schizophrenia sample (n = 711) and reported in Williams et al (2004) and the others typed with the bipolar sample. Duplicate samples were typed and allele coding verified. There were no significant deviations from Hardy-Weinberg equilibrium in neither the separate control sets nor in the pooled control set. The allele frequencies for each of the 3 SNPs showed no significant difference between the two control sets. Further, the two control samples had similar levels of linkage disequilibrium between the loci. Pooling the controls yielded a total sample of 1407 control individuals typed for 1 or more of the 3 loci (1178 typed for all loci).

Results for analysis of individual SNP genotyping in the bipolar disorder case-control sample are presented in Table 2. All markers showed genotype distributions consistent with Hardy-Weinberg equilibrium in both cases and controls ($p > .05$). Analyses of 3-locus haplotype provided no significant evidence for association. Similarly no differences in allele or genotype frequencies were seen between cases and controls for any of the polymorphisms (see Table 2).

We undertook analyses of subsets of the full bipolar sample for three psychosis-related phenotypes chosen a priori as likely to capture the areas of phenotypic overlap with schizophrenia.

Lifetime Occurrence of Psychotic Features. When we compared (against controls) the subset of bipolar cases in whom there was at least one known psychotic symptom at some time during the lifetime experience of illness, we found no significant differences in haplotype distributions (data not shown).

Psychosis in At Least Half of Mood Episodes. When we compared the subset of bipolar cases in whom psychotic features occurred in 50% or more of episodes of mood disorder, we did find nominally significant evidence for differences between the 3-locus haplotypes in cases and controls (p = .042; see Table 3). Inspection of the data revealed a pattern of results very similar to that observed previously in our schizophrenia data – both with

Table 2. Single-Marker and Haplotype Analysis for Markers P1655-P1635-SNPA in Case-Control Samples

Marker	Allele	Cases (n = 726) Frequency	Controls (n = 1407) Frequency	p Value
P1655	G	.472	.472	.999
	C	.528	.528	
P1635	G	.111	.114	.829
	A	.889	.886	
SNP A	T	.448	.433	.360
	A	.552	.567	
3 Marker-Haplotype (3 classes)[b]				
"Risk"		.152	.169	
"Protective"		.390	.383	.420
"Other"		.458	.448	
3 Marker-Haplotype[a] P1655-P1635-SNP A				
GAA		.086	.117	
CAA		.371	.361	
GGA		.091	.098	.076
GAT		.282	.244	
CAT		.152	.169	
GGT		.019	.021	

[a]Haplotypes with frequencies less than .01 were excluded.
[b]"Risk" haplotype: CAT; "Protective" haplotypes: CAA, GGT; "Other" haplotypes: All other haplotypes.

Table 3. Single-Marker and Haplotype Analysis for Markers P1655-P16353-SNPA in a Subset of Individuals with Psychotic Symptoms in 50% or More of Episodes Compared with Controls

Marker	Allele	Cases (n = 133) Frequency	Controls (n = 1407) Frequency	p Value
P1655	G	.495	.472	.415
	C	.505	.528	
P1635	G	.101	.114	.475
	A	.899	.886	
SNP A	T	.514	.433	.004[c]
	A	.486	.567	
3 Marker-Haplotype (3 classes)[b]				
"Risk"		.201	.169	
"Protective"		.315	.383	.042[d]
"Other"		.484	.448	
3 Marker-Haplotype[a]				
P1655-P1635-SNP A				
GAA		.098	.117	
CAA		.299	.361	
GGA		.084	.098	.079
GAT		.302	.244	
CAT		.201	.169	
GGT		.016	.021	

[a]Haplotypes with frequencies less than .01 were excluded.
[b]"Risk" haplotype: CAT; "Protective" haplotypes: CAA, GGT; "Other" haplotypes: All other haplotypes.
[c]Empirical p value = .0037.
[d]Empirical p value = .041.

SNP A (which on its own showed evidence for allelic association (p = .004)) and with the 3-locus haplotypes.

Predominantly Mood-Incongruent Psychotic Features. When we compared (against controls) the subset of bipolar cases in whom psychosis with predominantly mood incongruent psychotic features occurred, we found no significant differences in haplotype distributions (data not shown).

We also undertook exploratory analyses taking account of other subtypes and covariates but failed to identify evidence for a relationship with genetic variation at the polymorphisms and haplotypes studied. The additional sub-types examined were: a) lifetime occurrence of rapid cycling, b) lifetime occurrence of an episode of bipolar disorder (bipolar affective puerperal psychosis) occurring within 6 weeks of childbirth, c) onset before age 20 years, d) presence of family history of treated psychiatric illness in a first or second degree relative.

Discussion

In a large, well-characterized, UK Caucasian bipolar disorder case-control sample we have examined the 3 SNPs (P1655 (rs2619539), P1635 (rs3213207) and SNP A (rs2619538)) that previously gave the strongest association within our own schizophrenia case-control sample – sampled from the same UK Caucasian population and using similar recruitment and assessment methodology (Williams et al 2004).We found no evidence for association between this 3-locus haplotype in the *DTNBP1* gene and bipolar disorder in our full sample. Our full sample had excellent power to detect effect sizes of similar magnitude to those observed in our schizophrenia sample so we can be confident that the genetic variation observed at this 3-locus haplotype in the *DTNBP1* gene in our UK schizophrenia sample does not exert similar influence over susceptibility to bipolar disorder in general.

One of the characteristic features of schizophrenia is the presence of psychotic features and we, therefore, tested the hypothesis that variation at *DTNBP1* is associated with susceptibility to bipolar cases in which psychotic features occur in 50% or more of episodes of mood disorder ("Psychotic Bipolar Disorder") – a subset of our sample that is likely to capture potential phenotypic overlap with schizophrenia. Consistent with this hypothesis we found nominally significant evidence for association at the 3-locus haplotype and at one of the polymorphisms studied (SNPA) with a trend in haplotype and allele distributions similar to those observed in our previous studies of schizophrenia. In our schizophrenia sample, inspection of the individual haplotypes showed that those consisting of alleles C-A-T were significantly in excess in our cases (21% vs. 17%, i.e. "susceptibility"), while those consisting of C-A-A and G-G-T were significantly more common in controls (29% vs. 35% and < 1% vs. 3%, respectively, ie. "protective"), a finding replicated in the Irish schizophrenia sample that we examined. Interestingly, as with the two schizophrenia samples previously examined, the C-A-T "susceptibility" haplotype occurred at similar increased frequency in our Psychotic Bipolars (20%) compared with controls (17%) and the C-A-A "protective" haplotype at similar reduced frequency in Psychotic Bipolars (30%) compared with controls (36%) – raising the possibility that the genetic variation captured by these haplotypes influences susceptibility across the Kraepelinian dichotomy. However, it is noteworthy that the G-G-T haplotype which occurred in 2-3% of controls but extremely rarely in the schizophrenia cases (< 1%) did occur in our Bipolar sample at a frequency close to that in controls (>1.5% in the full Bipolar sample and in psychotic Bipolars) – suggesting that this haplotype could be associated with specific protection against the schizophrenia phenotype. This pattern of findings is of substantial interest but does not, on its own, provide compelling evidence for the involvement of *DTNBP1* in psychotic bipolar disorder. We chose the three psychosis-related phenotypes for our sub-analyses before examining the data and recognize that the precise choices were arbitrary. We should stress that our results are based on a modest number of cases of predominantly psychotic bipolar disorder (n = 133) and were not significant after correcting for multiple testing with the three psychosis-related phenotypic subsets. However, it is, of course the case, that the subsets of patients analyzed were substantially smaller than that in our full sample and, consequently our power to achieve significance in the subsets was more modest than in the full set (in our subset of 133 bipolar cases with predominantly psychotic episodes we had power of 74% at p = .05 to detect a haplotype effect similar to that observed in our schizophrenia sample). Furthermore, our psychosis-related phenotype definitions were not completely independent so a standard Bonferroni correction is conservative. After finding nominally significant evidence for association in the subset of bipolar cases with at least half the episodes having psychotic features, we explored the effect of analyses using other cut-offs for the proportion of psychotic features. We found that the maximal significance was achieved at a proportion of 45% of episodes having psychotic features (data not shown) – the significance, of course, reflects a balance between the effect size and the number of cases included.

It is of interest that a recent study of linkage disequilibrium using microsatellites in psychotic patients from a genetic isolate in Israel identified a region of significantly increased identity by descent sharing across the *dysbindin* gene region (Kohn et al 2004). Contributions to the signal came from patients with both

schizophrenia and mood diagnoses. The finding with relatively widely spaced microsatellite markers does not provide definitive information about *dysbindin* itself, but the data are consistent with the possibility that variation at *dysbindin* influences susceptibility to at least some cases of psychotic mood disorder as well as to schizophrenia.

Given that the pattern of our findings in the psychotic bipolars is similar to that in our schizophrenia sample, a possibility to consider is that our signals could be spurious and result from our control sample being unusual. However, this does not seem likely for the following reasons: a) Our findings are similar when we use either or both of the 2 waves of controls genotyped (ie. those genotyped with the schizophrenia cases and those with the bipolar cases), b) Our findings are similar when we use either the blood donor controls alone or the family practice controls alone, c) Our bipolar sample as a whole is very similar to the control sample – the association signals are generated by differences in the schizophrenia cases and the specific subset of bipolar psychotic cases.

It is clearly important that the specific hypothesis we have put forward about predominantly psychotic bipolar disorder is tested in independent samples – although it is to be expected that large samples will be required to provide a sufficiently sizable subset of patients with psychotic bipolar disorder to give adequate power. For example, approximately 200 bipolar cases with predominantly psychotic features and 1000 controls are required to give power of 80% to detect the effect sizes observed in our sample at a test size of $p < .05$ (Genetic Power Calculator; Purcell et al 2003). If the distribution of predominantly psychotic cases was similar to that in our own sample (ie. about 20% of cases) this would equate to a total bipolar sample of approximately 1000 individuals.

We have restricted our analysis to the 3 locus haplotype that showed strongest effect in our own schizophrenia sample. Our assumption is that this gave the greatest, a priori, likelihood of identifying a positive signal in our bipolar sample. However, it remains possible that variation elsewhere within or near *DTNBP1* could influence susceptibility to, or modify the course of bipolar disorder – either in general or to specific phenotypic subsets.

One interesting issue is the characteristics of the type of mood episode (ie. Manic or depressive) within the set of psychotic bipolars that could be influenced by variation at *dysbindin*. Within our sample the patients experienced roughly the same average number of episodes of mania and depression (mean 6.1, SD 9.0 episodes vs. mean 5.2, SD 9.3 episodes) but 95% of the cases had experienced at least one psychotic mania whereas only 46% had experienced at least one psychotic depression. Thus, our psychotic bipolar subset is characterized mainly by occurrence of episodes of psychotic mania.

It is important to comment that reported bipolar linkage data have not identified the 6p region as one of the favored chromosomal regions of interest for bipolar disorder (Nurnberger and Foroud 1999; Segurado et al 2003). Further, we found no linkage signal in this region in our own sib-pair linkage study (Bennett et al 2002) – although we acknowledge that a linkage signal is not a necessary condition for detection of linkage disequilibrium, as shown by our own schizophrenia findings at *dysbindin*.

The link between abnormal dysbindin function and schizophrenia – and perhaps psychotic bipolar disorder - is unclear. Dysbindin is expressed widely in the brain and other tissues (Straub et al 2002b). In brain, dysbindin binds β-dystobrevin. β-dystobrevin is itself a member of the dystrophin protein complex (DPC) found in post-synaptic densities (Austin et al 2000). Straub and colleagues postulated that compatible with the DPC's role in synaptic structure, maintenance and synaptic signaling, altered dysbindin/DPC function may lead to several of the structural and functional abnormalities that have been reported in schizophrenia, including altered function at glutamatergic and GABAergic synapses, and reduced synaptic density in frontal cortex and hippocampus (Straub et al 2002b). Recently, it has also been shown that mice that express no dystrophin (and therefore have altered DPC function) have abnormal development of the posterior cerebellar vermis (Baker et al 2002). The authors of that study postulated that similar abnormalities in cerebellar development as a result of altered dysbindin function may result in several of the other abnormalities that have been reported in psychosis including altered working memory, eye movement, and cerebellar structure (Baker et al 2002). However, Talbot and colleagues (2004) have shown that, contrary to expectations, dysbindin-1 is located presynaptically in glutamatergic neurons in the hippocampus and is reduced at these locations in schizophrenia. Moreover, this presynaptic location of dysbindin 1 appears to be independent of β-dystobrevin and, by implication, the DPC. The presynaptic function of dysbindin 1 is unknown but might include membership of a protein complex involved in the trafficking of lysosome related organelles (Owen et al 2004).

More genetic studies are required in order to, a) define precisely how genetic variation at this locus confers susceptibility to schizophrenia, and b) explore the breadth of disease phenotype influenced by this locus. However, there is a growing body of evidence to justify intensive investigations into disease mechanisms involving dysbindin.

In summary, we find no evidence that variation at the haplotype investigated in *DTNBP1* influences susceptibility to bipolar disorder in general. Our data are consistent with the possibility that this locus influences susceptibility to psychotic bipolar disorder in particular.

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