Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2010 March 5; 153B(2): 700–705. doi:10.1002/ajmg.b.31029.

No Association of Dysbindin With Symptom Factors of Schizophrenia in an Irish Case–Control Sample

Sarah E. Bergen^{1,2,*}, Ayman H. Fanous^{1,3,4,5}, Po-Hsiu Kuo⁶, Brandon K. Wormley^{1,3}, F. Anthony O'Neill⁷, Dermot Walsh⁸, Brien P. Riley^{1,2,3}, and Kenneth S. Kendler^{1,2,3}

¹Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia ²Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia ³Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia ⁴Washington VA Medical Center, Washington, District of Columbia ⁵Department of Psychiatry, Georgetown University Medical Center, Washington, District of Columbia ⁶Department of Public Health, National Taiwan University, Taipei, Taiwan ⁷Department of Mental Health, Queen's University, Belfast, Ireland ⁸Health Research Board, Dublin, Ireland

Abstract

Robust associations between the dysbindin gene (DTNBP1) and schizophrenia have been demonstrated in many but not all samples, and evidence that this gene particularly predisposes to negative symptoms in this illness has been presented. The current study sought to replicate the previously reported negative symptom associations in an Irish case–control sample. Association between dysbindin and schizophrenia has been established in this cohort, and a factor analysis of the assessed symptoms yielded three factors, Positive, Negative, and Schneiderian. The sequential addition method was applied using UNPHASED to assess the relationship between these symptom factors and the high-risk haplotype. No associations were detected for any of the symptom factors indicating that the dysbindin risk haplotype does not predispose to a particular group of symptoms in this sample. Several possibilities, such as differing risk haplotypes, may explain this finding.

Keywords

modifier; sequential addition; negative symptoms

Schizophrenia is a severe neuropsychiatric disorder affecting approximately 1% of the global population. Despite decades of research, conclusive facts regarding the etiology of schizophrenia have remained elusive. However, a substantial genetic underpinning is indicated by a meta-analysis-derived heritability estimate of 81% [Sullivan et al., 2003], and evidence is mounting for some susceptibility genes. Dysbindin (dystrobrevin-binding protein 1; DTNBP1) in particular is one of the most promising candidate genes for schizophrenia to date [Sun et al., 2008] with numerous positive associations reported [Straub et al., 2002; van den Oord et al., 2003b; Schwab et al., 2003; Funke et al., 2004; Kirov et al., 2004; Williams et al., 2004; Fallin et al., 2005; Li et al., 2005; Tochigi et al., 2006; Duan et al., 2007; Tosato et al., 2007; Vilella et al., 2007] but several negative reports, as well [Morris et al., 2003; Hall et al., 2004; Li et al., 2005; Holliday et al., 2006; Joo et al., 2006;

Bakker et al., 2004; Datta et al., 2007; Liu et al., 2007; Pedrosa et al., 2007; Turunen et al., 2007; Wood et al., 2007; Zinkstok et al., 2007].

Of the many studies reporting associations between schizophrenia and dysbindin, most have genotyped somewhat different markers, and considerable heterogeneity in risk haplotypes has been reported. Variability in study design has hampered attempts at cross-study interpretation. One recent meta-analysis failed to find allelic heterogeneity [Mutsuddi et al., 2006], while another more recent meta-analysis did uncover substantial allelic heterogeneity for the DTNBP1-schizophrenia association [Maher et al., submitted]. Marker single nucleotide polymorphism (SNP) A did attain overall significance in this report [Maher et al., submitted], and another meta-analysis of associations reported in the SzGene database found SNP rs1011313 to be significantly associated in Caucasian populations [Allen et al., 2008].

Some aspects of the dysbindin protein functions have been elucidated including its role in the biogenesis of organelles such as lysosomes, melanosomes, and platelet dense granules [Dell'Angelica, 2004]. The mouse homologue of dysbindin binds to alpha and beta-dystrobrevins in muscle tissues [Benson et al., 2001], and dysbindin has also been localized to glutamatergic presynaptic terminals in humans [Talbot et al., 2004]. The mechanism by which dysbindin polymorphisms impact the liability to schizophrenia is unknown, but affected subjects have shown reduced protein and mRNA expression in brain regions implicated in this disorder such as the hippocampus [Talbot et al., 2004; Weickert et al., 2008], the prefrontal cortex, and a non-significant reduction in the midbrain [Weickert et al., 2004]. A study examining prefrontal and hippocampal dysbindin expression levels in mice treated with common antipsychotic medications revealed unchanged mRNA levels compared to an untreated group suggesting that the changes observed in human populations are unlikely to be due to the effects of medication [Chiba et al., 2006].

Prior reports have linked dysbindin with negative symptoms in schizophrenia. Fanous et al. [2005] examined the relationship of dysbindin with clinical features of schizophrenia in a sample of 270 multiply affected Irish families, containing no overlapping individuals with the present cohort. Dysbindin's role as a susceptibility gene in this sample had been previously established [Straub et al., 2002], and further examination revealed that subjects in the upper 40th percentile for negative symptoms were significantly more likely to have the high-risk haplotype. This was in contrast to the other four symptom factors, hallucinations, delusions, manic, and depressive symptoms, which showed no association with the haplotype of interest.

DeRosse et al. [2006] also reported association of a dysbindin risk haplotype (Table I) and negative symptoms in 181 Caucasian men and women with schizophrenia, covarying for neurocognitive functioning. This cohort (and healthy volunteers) had also shown association between this haplotype and neurocognitive dysfunction [Burdick et al., 2006]. Although decreased intellectual functioning often accompanies negative symptoms, these studies suggest there may be at least partially separable effects. Another relevant study of 262 Irish patients with schizophrenia found lower scores on a "hostility/excitability" factor and a trend for higher negative symptom scores in subjects with a "CAT" dysbindin risk haplotype [Table I; Corvin et al., 2008].

In the Irish Case-Control Study of Schizophrenia (ICCSS), an association between the dysbindin haplotype GCACTT (Table I) and schizophrenia has been found (case frequency: 0.454, control frequency: 0.388, $\chi^2=13.561$, $P=0.0002$) [Riley et al., submitted]. The current study explores the relationship between this haplotype and the clinical symptoms of schizophrenia in the same subjects.

Cases from the ICCSS were collected from in-patient and out-patient psychiatric facilities in the Republic of Ireland and Northern Ireland. Subjects were eligible for inclusion if they had a diagnosis of schizophrenia or poor-outcome schizoaffective disorder by DSM-III-R criteria. Subjects were eligible for inclusion and interviewed between April 1987 and November 1992 if they had a diagnosis of schizophrenia or poor-outcome schizoaffective disorder by DSM-III-R criteria, which were confirmed by a blind expert diagnostic review. Control subjects, selected from several sources, including blood donation centers, were included if they denied a lifetime history of schizophrenia. Both cases and controls were included only if they reported all four grandparents as being born in Ireland or the United Kingdom (Chen et al., 2008). In this study, 625 control subjects were used in conjunction with 730, 868, and 675 affected subjects for the Positive, Negative, and Schneiderian symptom factor analyses, respectively.

Subjects were rated for each symptom using interviews, derived from the expanded psychosis section of the Structured Clinical Interview for DSM-III-R (SCID) [Spitzer and Williams, 1985], and case records independently. These two assessments were averaged and entered into a factor analysis using the statistical program MPlus [Muthen and Muthen, 2001]. This yielded three symptom factors: Positive, Negative, and Schneiderian. Sum scores were generated for each factor with eleven items used to generate Positive and Schneiderian symptom scores and eight for Negative symptoms. The items were scaled using different numbers of levels (e.g., 1–4 or 1–5) then combined and standardized to have values ranging from one to two. Example items loading on the Positive symptom factor included Visual and Somatic Hallucinations and Grandiose Delusions. The Schneiderian symptom factor incorporated Thought Withdrawal and Broadcasting and Voices Discussing items, and the Negative symptom factor included items such as Alogia, Avolition, and Affective Flattening.

We genotyped a total of 12 SNPs in *DTNBPI* which is transcribed in opposite orientation to the human genome sequence. Markers were selected from those included in previous reports from our group and others, and were chosen to allow reconstruction of the specific haplotypes widely observed in this locus [van den Oord et al., 2003a].

All markers were genotyped using fluorescence polarization detection of template-directed dye-terminator incorporation (FP-TDI). We used the AcycloPrime SNP detection kits appropriate for the specific polymorphism (PerkinElmer Life Sciences, Boston, MA) and manufacturer's instructions. Genotypes were called using an automated allele scoring platform [van den Oord et al., 2003b]. PCR and single-base extension primers were designed manually and are available on request. The average genotyping completion rate was 94.7% (range 89.3–98.7%).

We used a sequential addition approach well suited to data such as these in which a quantitative trait is measured in cases but not controls [Macgregor et al., 2006]. Briefly, this method consists of an initial Chi-square test between all cases and controls evaluating risk allele or haplotype proportions between groups. Next, the cases with the highest level of the quantitative trait are analyzed against all controls and the resulting Chi-square value is compared to that for the full sample. Subjects with progressively lower levels of the quantitative trait are incorporated into the case group until the Chi-square statistic meets or exceeds that of the full sample. For these analyses, we used the sum scores for the three symptom factors, Positive, Negative, and Schneiderian, as the quantitative traits and the previously determined risk haplotype, GCACTT, defined by the minor allele of rs2619538 and the major alleles of rs1474605, rs1018381, rs2619522, rs760761, and rs2005976 [Riley et al., submitted]. All analyses were implemented using SAS [SAS Institute Inc, 2005] and UNPHASED [Dudbridge, 2003].

Linear regression analyses were also utilized to assess potential relationships between symptom factors and the high-risk dysbindin haplotype. Using only data from the affected subjects, scores for each factor were separately regressed against the high-risk haplotype. Additionally, *t*-tests of sum scores for each factor by risk haplotype carrier status were performed using SAS [SAS Institute Inc, 2005].

We found no association of the high-risk dysbindin haplotype with any of the symptom factors using sequential addition. While the Negative symptom factor sequential addition analyses did ultimately yield a Chi-square value exceeding the full sample Chi-square value, 84% of the cases were incorporated into the analyses before this was accomplished. There is no established cutoff for the percentage of included case subjects necessary to demonstrate association; however, with such a high percentage of cases used, a strong association with negative symptoms no longer seems plausible. Additionally, no relationships between the risk haplotype and symptom factors were found using linear regression (Negative $P=0.53$, Positive $P=0.51$, Schneiderian $P=0.96$) or *t*-tests (Negative $P=0.52$, Positive $P=0.54$, Schneiderian $P=0.78$) (Table II).

None of the symptom factors analyzed demonstrated an association with the dysbindin risk haplotype in this cohort. This was unexpected considering two prior studies examining negative symptoms and dysbindin did find an association [Fanous et al., 2005; DeRosse et al., 2006], but several possible reasons may account for this discrepancy.

First, the symptom factor structure differed between the Irish family sample and the present Irish case-control sample. For the three symptom factors used here, negative symptoms were possibly more broadly defined than for the Irish family sample which had five symptom factors, and the items in each differed as a result of the instruments used. Three items were similar across samples: inappropriate affect, affective flattening, and thought disorder. Negative symptoms in this sample included four additional items and in the Irish family sample, eight more items. DeRosse et al. (2006) used only three items, affective flattening, alogia, and avolition, all of which were incorporated into the negative symptom factor in the present study.

Additionally, the high-risk haplotypes defined in the Irish samples are highly cladistically divergent from each other. It is conceivable that one haplotype only confers risk to schizophrenia while the other predisposes to schizophrenia as well as a high degree of negative symptoms. Another possibility is that the dysbindin haplotype association with negative symptoms is actually driven by linkage disequilibrium with an evolutionarily recent, causal polymorphism.

Manifestations of schizophrenia involving a high degree of negative symptoms are often considered the most severe. Negative symptoms are among the most persistent and refractory to treatment, making these symptoms imperative to examine [Stahl and Buckley, 2007]. Since prior reports of modification by dysbindin have included negative symptoms [Fanous et al., 2005; DeRosse et al., 2006], cognitive function [Burdick et al., 2007; Donohoe et al., 2007], low hostility/excitability [Corvin et al., 2008] and poor clinical outcome [Tosato et al., 2007], this suggests two distinct possibilities. First, all of these interrelated disease dimensions may be tapping a common physiological process partially underlying each of them. Alternatively, of the various dysbindin haplotypes that have been associated with schizophrenia, they may have distinct symptom modifying properties or none at all. Dysbindin variation has also been associated with cognitive function in normal individuals [Burdick et al., 2007; Luciano et al., 2009].

Continuing efforts to explore the genetic underpinnings of clinical variation in schizophrenia are vital to understanding and treating this disorder. Advances in identifying susceptibility

genes have been hindered by genetic and clinical heterogeneity, but understanding the nature and extent of the relationship between them may bring us closer to a useful comprehension of schizophrenia.

Acknowledgments

The subjects, staff, and facilities of Ireland contributing to the ICCSS are gratefully acknowledged for their essential roles. Funding for this project was provided by Department of Veterans Affairs Merit Review Program grant to AHF, a research grant (RO1MH41953) to KSK from the National Institute of Mental Health (NIMH), a research grant from the NARSAD to PHK, and a training grant (NIMH 20030) supporting SEB.

Grant sponsor: Department of Veterans Affairs Merit Review Program; Grant sponsor: National Institute of Mental Health (NIMH); Grant number: RO1MH41953; Grant sponsor: NARSAD.

REFERENCES

- Allen NC, Bagade S, McQueen MB, Ioannidis JP, Kavvoura FK, Khoury MJ, Tanzi RE, Bertram L. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: The SzGene database. *Nat Genet* 2008;40(7):827–834. [PubMed: 18583979]
- Bakker SC, Hoogendoorn ML, Selten JP, Verduijn W, Pearson PL, Sinke RJ, Kahn RS. Neuregulin 1: Genetic support for schizophrenia subtypes. *Mol Psychiatry* 2004;9:1061–1063. [PubMed: 15303101]
- Benson MA, Newey SE, Martin-Rendon E, Hawkes R, Blake DJ. Dysbindin, a novel coiled-coil-containing protein that interacts with the dystrobrevins in muscle and brain. *J Biol Chem* 2001;276:24232–24241. [PubMed: 11316798]
- Burdick KE, Lencz T, Funke B, Finn CT, Szeszko PR, Kane JM, Kucherlapati R, Malhotra AK. Genetic variation in DTNBP1 influences general cognitive ability. *Hum Mol Genet* 2006;15:1563–1568. [PubMed: 16415041]
- Burdick KE, Goldberg TE, Funke B, Bates JA, Lencz T, Kucherlapati R, Malhotra AK. DTNBP1 genotype influences cognitive decline in schizophrenia. *Schizophr Res* 2007;89:169–172. [PubMed: 17074466]
- Chen Q, Wang X, O'Neill FA, Walsh D, Fanous A, Kendler KS, Chen X. Association study of CSF2RB with schizophrenia in Irish family and Case-control samples. *Mol Psychiatry* 2008;13(10):930–938. [PubMed: 17667962]
- Chiba S, Hashimoto R, Hattori S, Yohda M, Lipska B, Weinberger DR, Kunugi H. Effect of antipsychotic drugs on DISC1 and dysbindin expression in mouse frontal cortex and hippocampus. *J Neural Transm* 2006;113:1337–1346. [PubMed: 16463116]
- Corvin A, Donohoe G, Nangle JM, Schwaiger S, Morris D, Gill M. A dysbindin risk haplotype associated with less severe manic-type symptoms in psychosis. *Neurosci Lett* 2008;431:146–149. [PubMed: 18162312]
- Datta SR, McQuillin A, Puri V, Choudhury K, Thirumalai S, Lawrence J, Pimm J, Bass N, Lamb G, Moorey H, Morgan J, Punukollu B, Kandasami G, Kirwin S, Sule A, Quesed D, Curtis D, Gurling HM. Failure to confirm allelic and haplotypic association between markers at the chromosome 6p22.3 dystrobrevin-binding protein 1 (DTNBP1) locus and schizophrenia. *Behav Brain Funct* 2007;3:50. [PubMed: 17888175]
- Dell'Angelica EC. The building BLOC(k)s of lysosomes and related organelles. *Curr Opin Cell Biol* 2004;16:458–464. [PubMed: 15261680]
- DeRosse P, Funke B, Burdick KE, Lencz T, Ekholm JM, Kane JM, Kucherlapati R, Malhotra AK. Dysbindin genotype and negative symptoms in schizophrenia. *Am J Psychiatry* 2006;163:532–534. [PubMed: 16513878]
- Donohoe G, Morris DW, Clarke S, McGhee KA, Schwaiger S, Nangle JM, Garavan H, Robertson IH, Gill M, Corvin A. Variance in neuro-cognitive performance is associated with dysbindin-1 in schizophrenia: A preliminary study. *Neuropsychologia* 2007;45:454–458. [PubMed: 16930638]

- Duan J, Martinez M, Sanders AR, Hou C, Burrell GJ, Krasner AJ, Schwartz DB, Gejman PV. DTNBP1 (Dystrobrevin binding protein 1) and schizophrenia: Association evidence in the 3' end of the gene. *Hum Hered* 2007;64:97–106. [PubMed: 17476109]
- Dudbridge F. Pedigree disequilibrium tests for multilocus haplotypes. *Genet Epidemiol* 2003;25:115–121. [PubMed: 12916020]
- Fallin MD, Lasseter VK, Avramopoulos D, Nicodemus KK, Wolyniec PS, McGrath JA, Steel G, Nestadt G, Liang KY, Hagan RL, Valle D, Pulver AE. Bipolar I disorder and schizophrenia: A 440-single-nucleotide polymorphism screen of 64 candidate genes among Ashkenazi Jewish case-parent trios. *Am J Hum Genet* 2005;77:918–936. [PubMed: 16380905]
- Fanous AH, van den Oord EJ, Riley BP, Aggen SH, Neale MC, O'Neill FA, Walsh D, Kendler KS. Relationship between a high-risk haplotype in the DTNBP1 (dysbindin) gene and clinical features of schizophrenia. *Am J Psychiatry* 2005;162:1824–1832. [PubMed: 16199828]
- Funke B, Finn CT, Plocik AM, Lake S, DeRosse P, Kane JM, Kucherlapati R, Malhotra AK. Association of the DTNBP1 locus with schizophrenia in a U.S. population. *Am J Hum Genet* 2004;75:891–898. [PubMed: 15362017]
- Hall D, Gogos JA, Karayiorgou M. The contribution of three strong candidate schizophrenia susceptibility genes in demographically distinct populations. *Genes Brain Behav* 2004;3:240–248. [PubMed: 15248869]
- Holliday EG, Handoko HY, James MR, McGrath JJ, Nertney DA, Tirupati S, Thara R, Levinson DF, Hayward NK, Mowry BJ, Nyholt DR. Association study of the dystrobrevin-binding gene with schizophrenia in Australian and Indian samples. *Twin Res Hum Genet* 2006;9:531–539. [PubMed: 16899160]
- Joo EJ, Lee KY, Jeong SH, Ahn YM, Koo YJ, Kim YS. The dysbindin gene (DTNBP1) and schizophrenia: No support for an association in the Korean population. *Neurosci Lett* 2006;407:101–106. [PubMed: 16959423]
- Kirov G, Ivanov D, Williams NM, Preece A, Nikolov I, Milev R, Koleva S, Dimitrova A, Toncheva D, O'Donovan MC, Owen MJ. Strong evidence for association between the dystrobrevin binding protein 1 gene (DTNBP1) and schizophrenia in 488 parent-offspring trios from Bulgaria. *Biol Psychiatry* 2004;55:971–975. [PubMed: 15121479]
- Li T, Zhang F, Liu X, Sun X, Sham PC, Crombie C, Ma X, Wang Q, Meng H, Deng W, Yates P, Hu X, Walker N, Murray RM, St. Clair D, Collier DA. Identifying potential risk haplotypes for schizophrenia at the DTNBP1 locus in Han Chinese and Scottish populations. *Mol Psychiatry* 2005;10:1037–1044. [PubMed: 16044171]
- Liu CM, Liu YL, Fann CS, Yang WC, Wu JY, Hung SI, Chen WJ, Chueh CM, Liu WM, Liu CC, Hsieh MH, Hwang TJ, Faraone SV, Tsuang MT, Hwu HG. No association evidence between schizophrenia and dystrobrevin-binding protein 1 (DTNBP1) in Taiwanese families. *Schizophr Res* 2007;93:391–398. [PubMed: 17407805]
- Luciano M, Miyajima F, Lind PA, Bates TC, Horan M, Harris SE, Wright MJ, Ollier WE, Hayward C, Pendleton N, Gow AJ, Visscher PM, Starr JM, Deary IJ, Martin NG, Payton A. Variation in the dysbindin gene and normal cognitive function in three independent population samples. *Genes Brain Behav* 2009;8:218–227. [PubMed: 19077176]
- Macgregor S, Craddock N, Holmans PA. Use of phenotypic covariates in association analysis by sequential addition of cases. *Eur J Hum Genet* 2006;14:529–534. [PubMed: 16538225]
- Maher BS, Reimers MA, Riley BP, Kendler KS. Allelic heterogeneity in genetic association meta-analysis: An application to DTNBP1 and schizophrenia. *Human Heredity*. In press.
- Morris DW, McGhee KA, Schwaiger S, Scully P, Quinn J, Meagher D, Waddington JL, Gill M, Corvin AP. No evidence for association of the dysbindin gene [DTNBP1] with schizophrenia in an Irish population-based study. *Schizophr Res* 2003;60:167–172. [PubMed: 12591580]
- Muthen, LK.; Muthen, BO. User's Guide. Los Angeles: Muthen and Muthen; 2001. Mplus: Statistical Analysis with Latent Variables.
- Mutsuddi M, Morris DW, Waggoner SG, Daly MJ, Scolnick EM, Sklar P. Analysis of high-resolution HapMap of DTNBP1 (Dysbindin) suggests no consistency between reported common variant associations and schizophrenia. *Am J Hum Genet* 2006;79:903–909. [PubMed: 17033966]

- Pedrosa E, Ye K, Nolan KA, Morrell L, Okun JM, Persky AD, Saito T, Lachman HM. Positive association of schizophrenia to JARID2 gene. *Am J Med Genet Part B* 2007;144B:45–51. [PubMed: 16967465]
- Riley BP, Kuo PH, Maher BS, Fanous AH, Sun J, Wormley BK, O'Neill FA, Walsh D, Zhao Z, Kendler KS. The dystrobrevin binding protein 1 (DTNBP1) gene is associated with schizophrenia in the Irish Case Control Study of Schizophrenia (ICCS) sample. Submitted to Schizophrenia Research.
- SAS Institute Inc. SAS software version 9.1.3. Cary, NC: Ref Type: Computer Program; 2005.
- Schwab SG, Knapp M, Mondabon S, Hallmayer J, Borrmann-Hassenbach M, Albus M, Lerer B, Rietschel M, Trixler M, Maier W, Wildenauer DB. Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. *Am J Hum Genet* 2003;72:185–190. [PubMed: 12474144]
- Spitzer, RL.; Williams, JBW. Structured clinical interview for DSM-III-R (SCID). New York: Biometrics Research Department, New York State Psychiatric Institute; 1985.
- Stahl SM, Buckley PF. Negative symptoms of schizophrenia: A problem that will not go away. *Acta Psychiatr Scand* 2007;115:4–11. [PubMed: 17201860]
- Straub RE, Jiang Y, MacLean CJ, Ma Y, Webb BT, Myakishev MV, Harris-Kerr C, Wormley B, Sadek H, Kadambi B, Cesare AJ, Gibberman A, Wang X, O'Neill FA, Walsh D, Kendler KS. Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. *Am J Hum Genet* 2002;71:337–348. [PubMed: 12098102]
- Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry* 2003;60:1187–1192. [PubMed: 14662550]
- Sun J, Kuo PH, Riley BP, Kendler KS, Zhao Z. Candidate genes for schizophrenia: A survey of association studies and gene ranking. *Am J Med Genet Part B* 2008;147B(7):1173–1181. [PubMed: 18361404]
- Talbot K, Eidem WL, Tinsley CL, Benson MA, Thompson EW, Smith RJ, Hahn CG, Siegel SJ, Trojanowski JQ, Gur RE, Blake DJ, Arnold SE. Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. *J Clin Invest* 2004;113:1353–1363. [PubMed: 15124027]
- Tochigi M, Zhang X, Ohashi J, Hibino H, Otowa T, Rogers M, Kato T, Okazaki Y, Kato N, Tokunaga K, Sasaki T. Association study of the dysbindin (DTNBP1) gene in schizophrenia from the Japanese population. *Neurosci Res* 2006;56:154–158. [PubMed: 16876895]
- Tosato S, Ruggeri M, Bonetto C, Bertani M, Marrella G, Lasalvia A, Cristofalo D, Aprili G, Tansella M, Dazzan P, Diforti M, Murray RM, Collier DA. Association study of dysbindin gene with clinical and outcome measures in a representative cohort of Italian schizophrenic patients. *Am J Med Genet Part B* 2007;144B:647–659. [PubMed: 17290445]
- Turunen JA, Peltonen JO, Pietilainen OP, Hennah W, Loukola A, Paunio T, Silander K, Ekelund J, Varilo T, Partonen T, Lonnqvist J, Peltonen L. The role of DTNBP1, NRG1, and AKT1 in the genetics of schizophrenia in Finland. *Schizophr Res* 2007;91:27–36. [PubMed: 17300918]
- van den Oord EJ, Jiang Y, Riley BP, Kendler KS, Chen X. FP-TDI SNP scoring by manual and statistical procedures: A study of error rates and types. *Biotechniques* 2003a;34:610–620. 622. [PubMed: 12661166]
- van den Oord EJ, Sullivan PF, Jiang Y, Walsh D, O'Neill FA, Kendler KS, Riley BP. Identification of a high-risk haplotype for the dystrobrevin binding protein 1 (DTNBP1) gene in the Irish study of high-density schizophrenia families. *Mol Psychiatry* 2003b;8:499–510. [PubMed: 12808430]
- Vilella E, Costas J, Sanjuan J, Guitart M, De Diego Y, Carracedo A, Martorell L, Valero J, Labad A, De Frutos R, Najera C, Molto MD, Toirac I, Guillamat R, Brunet A, Valles V, Perez L, Leon M, de Fonseca FR, Phillips C, Torres M. Association of schizophrenia with DTNBP1 but not with DAO, DAOA, NRG1 and RGS4 nor their genetic interaction. *J Psychiatr Res* 2008;42:278–288. [PubMed: 17408693]
- Weickert CS, Straub RE, McClintock BW, Matsumoto M, Hashimoto R, Hyde TM, Herman MM, Weinberger DR, Kleinman JE. Human dysbindin (DTNBP1) gene expression in normal brain and in schizophrenic prefrontal cortex and midbrain. *Arch Gen Psychiatry* 2004;61:544–555. [PubMed: 15184234]

- Weickert CS, Rothmond DA, Hyde TM, Kleinman JE, Straub RE. Reduced DTNBP1 (dysbindin-1) mRNA in the hippocampal formation of schizophrenia patients. *Schizophr Res* 2008;98:105–110. [PubMed: 17961984]
- Williams NM, Preece A, Morris DW, Spurlock G, Bray NJ, Stephens M, Norton N, Williams H, Clement M, Dwyer S, Curran C, Wilkinson J, Moskvina V, Waddington JL, Gill M, Corvin AP, Zammit S, Kirov G, Owen MJ, O'Donovan MC. Identification in 2 independent samples of a novel schizophrenia risk haplotype of the dystrobrevin binding protein gene (DTNBP1). *Arch Gen Psychiatry* 2004;61:336–344. [PubMed: 15066891]
- Wood LS, Pickering EH, Dechairo BM. Significant support for DAO as a schizophrenia susceptibility locus: Examination of five genes putatively associated with schizophrenia. *Biol Psychiatry* 2007;61:1195–1199. [PubMed: 17055463]
- Zinkstok JR, de Wilde O, van Amelsvoort TA, Tanck MW, Baas F, Linszen DH. Association between the DTNBP1 gene and intelligence: A case-control study in young patients with schizophrenia and related disorders and unaffected siblings. *Behav Brain Funct* 2007;3:19. [PubMed: 17445278]

TABLE I

Dysbindin Risk Haplotypes With Phenotypic Associations by Study

	rs2619538	rs909706	rs1474605	rs1018381	rs2619522	rs760761	rs2005976	rs2619528	rs1011313	rs3213207	rs2619539
Present study	T		T	C	A	C	G				
Fanous et al. [2005]			G	C	G	T	A	A	G	G	
DeRosse et al. [2006]		G		T	G	T		A	G		
Corvin et al. [2008]	T									A	C
Tosato et al. [2007]	A	A									

TABLE II

Sum Score Statistics for All Factors by Risk Haplotype Carrier Status

Factor	Carrier status	Subjects	Mean	SD	t	P-value
Negative symptoms	Non-Carriers	181	1.507	0.37	-0.65	0.5156
	Carriers	435	1.528	0.35		
Positive symptoms	Non-Carriers	163	1.516	0.34	0.61	0.5439
	Carriers	375	1.498	0.33		
Schneiderian symptoms	Non-Carriers	137	1.502	0.35	-0.27	0.7846
	Carriers	330	1.512	0.34		