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As young children, we are told that plants need water and sunlight to grow, opposites attract, and whatever goes up must come down. These fundamental basics gradually gain meaning as we explore the depths of science throughout our elementary and eventually high school courses. However, there are questions that even our esteemed teachers and professors do not know how to answer; what causes cancer, how to determine the age of a brown dwarf in the solar system, and why obesity is running rampant through our American youth.

When I entered 9th grade in a new school, tackling a broad expanse of advanced science and mathematics courses, I took note of the extent of questions that could not merit a simple answer. Sometimes science is more complex than the average mind. An advanced science research program offered allowed me to take these questions and seek answers. I read through hundreds of published journals to learn about the scientific procedure and the methodology that research entails. Being that I am a twin, I sought after genetic studies to quench my rooted fascination with the potential biological linkage between family members, and furthermore, siblings. People would constantly question an existence of some bizarre twin connection; if your brother has to sneeze, will you have to as well? No—but could that be possible? If he develops a rare disorder, will I become susceptible as the next victim? As I explored the complexity of human psychology in association with genetic variability, I was amazed at the myriad of possibilities, both inheritable and environmentally stimulating, that may cause the onset of schizophrenia. A rare psychological and developmental disorder that develops in the late teen years, schizophrenia has no defined causes and no curability. Effective treatment is both

expensive and dangerous. Urged to act on my scientific curiosity and concern for change, I sought after a research prospect.

High school students are not typically offered the opportunity to conduct research at a graduate and/or professional level. In order to become a part of the scientific community, I embarked on a personal journey to contact leading professionals in my field of interest. Sending an overabundance of e-mails and making numerous phone calls, I found myself interviewing with published professors and scientists, many of which had published the articles that had inspired me to begin my own research in the first place. My efforts paid off and I was proud of myself as I landed an internship with leading researchers at the Zucker Hillside Hospital in Glen Oaks, New York. Over the course of two years, I engrossed myself in patient's files, medical records, neurological tests results, and genotyping data. Subsequent studies allowed me to explore the illness in terms of its epidemiology, as per a haplotype in the Dysbindin gene, and its potential for treatment, according to compatibility with an atypical antipsychotic medication called Clozapine. I learned statistical methods to test the significance of my research, allowing me to perform a stepwise multiple regression analysis that ultimately yielded significant results.

The following journal is a culminating representation of the research I conducted, entitled "Dysbindin (*DTNBP1*) Haplotype, Family History of Psychiatric Illness, and Lifetime Severity of Negative Psychotic Symptoms in Patients with Schizophrenia." I hope that my research project will inspire students to take a scientific query and seek a way to find answers. Even if such a journey should seem beyond reach or insignificant to the totality of science in general, never doubt the ability to learn new things and advance

the scientific community with even a negative finding. Too many questions linger unanswered day in and day out; but as an emphasis on science and technology advances, the potential for answers will only strengthen.

Dysbindin (*DTNBP1*) Haplotype, Family History of Psychiatric Illness, and Lifetime Severity of Negative Psychotic Symptoms in Patients with Schizophrenia

Schizophrenia is a serious and disabling neuropsychiatric disorder characterized by disturbances in behavioral, cognitive and perceptual functions (Kendler, 2004). It affects approximately 1% of the general population and often has devastating effects on the patients, their families and the community. Although the underlying pathology of schizophrenia is not fully understood, adoption and twin studies indicate that genetic factors play a substantial role in the etiology of the disease (Straub, et al., 1995).

Among the genes linked to schizophrenia, the gene encoding for dysbindin has proven to have one of the strongest associations to date (Schwab, et al., 2003; Funke, et al., 2004). Straub and colleagues (1995) were the first to identify a significant linkage peak on chromosome 6p in 270 Irish high-density schizophrenia pedigrees. Subsequent work by the same group narrowed the location to several variants in the gene coding for dysbindin at 6p22.3 (Straub, et al., 2002). Dysbindin is an evolutionarily conserved protein that binds alpha and beta dystrobrevin, components of the dystrophin glycoprotein complex (DPC) (Benson, et al., 2001). Dysbindin mRNA is expressed widely in the human brain, including regions in the frontal cortex, temporal cortex, hippocampus, caudate, putamen, nucleus accumbens, amygdala, thalamus, and midbrain (Weickert, et al., 2004). Although the functional role of dysbindin is not yet fully understood, many research groups have replicated the association between variation

within the dysbindin gene (*DTNBP1*) and schizophrenia (Schwab, et al., 2003; Funke, et al., 2004; Williams, et al., 2004; Bray, et al., 2005). More recently, findings relating *DTNBP1* to schizophrenia have indicated that variation within the gene may contribute to the etiology of a subtype of schizophrenia that is primarily characterized by cognitive impairment (Burdick, et al., 2006; Williams, et al., 2004) and negative symptoms (DeRosse, et al, 2006; Fanous, et al., 2005).

Cognitive dysfunction is common in schizophrenia and may account for a substantial portion of the functional impairment associated with the illness (Bowie and Harvey, 2005). Although the genetic contributions to specific domains of cognitive dysfunction are not yet well characterized, it has long been known that general intelligence is heritable (Plomin & Spinath, 2004). Recently, Posthuma and colleagues (2005) have found an association between a region on chromosome 6p and general cognitive abilities in healthy subjects. Further, Hallmayer and colleagues (2005) reported that the linkage of schizophrenia to a region of 6p identified was specific to a subset of patients who were characterized by general cognitive deficits. This positional evidence indicating an association between cognitive functioning and variation within regions of 6p, combined with demonstrations of an association between schizophrenia and a gene encompassed within this region, *DTNBP1*, suggests that *DTNBP1* may be associated with the cognitive dysfunction often noted in patients with schizophrenia. This hypothesis is further substantiated by findings indicating that carriers of a previously identified schizophrenia risk haplotype within *DTNBP1* (Funke, et al. 2004) had significantly lower scores on a measure of general cognitive abilities than non-carriers. Specifically, Burdick and colleagues (2006) used a measure of general intelligence, Spearman's *g*, to test for an

association between cognitive abilities and variation in *DTNBPI*. Charles Spearman, who first accounted for the psychometric definition of intelligence in the early 20th century, described a measure of ‘general cognitive ability’ (Spearman’s *g*) that could be extracted from a principal component analysis (PCA) score and is based on significant covariance, or phenotypic overlap, of a number of different cognitive processes, including memory, spatial ability and verbal ability (Plomin, 1999). This measure has been demonstrated to account for approximately 40% of the variance in performance on diverse cognitive measures (Carroll, 1997). Using *g* as the primary dependent measure, Burdick et al. (2006) found that carriers of the *DTNBPI* risk haplotype (CTCTAC) identified by Funke et al. (2004) scored significantly lower on *g* than non-carriers. This relation was demonstrated in both healthy subjects and patients suffering from schizophrenia.

Cognitive dysfunction in schizophrenia is often accompanied by negative symptoms, such as affective flattening, thought impoverishment, and avolition (Mortimer & Spense, 2003). It has been suggested that this relation between cognitive function and negative symptoms may represent different manifestations of a common underlying pathophysiology. Thus, factors contributing to cognitive deficits may also contribute to negative symptomatology. Recent evidence linking the CTCTAC *DTNBPI* risk haplotype (DeRosse, et al., 2006) and variants within this haplotype (Fanous, et al., 2005) with negative symptoms in schizophrenia provides support for this suggestion.

Cognitive deficits and negative symptoms often appear one to two years prior to the identification and diagnosis of the illness. Though not well understood, this retrospectively defined period, known as the ‘prodromal’ illness (DSM-IV), is typically characterized by a standardized course of symptoms. Patients first encounter nonspecific

symptoms, followed by negative symptoms and finally positive symptoms. Patients often experience deterioration in school performance, emotional health (including mood and sleep problems), hygiene, and social capacity and interest (Talbot, et al., 2004). Based on the association of *DTNBPI* to the symptoms that characterize this prodromal period, it is possible that the effect of *DTNBPI* variation is related to the insidious onset of schizophrenia, characterized as early as the prodromal period.

To determine the role of premorbid indicators in illness onset, Cannon et al. (1997) compared 70 patients with schizophrenia and 28 patients with bipolar disorder to healthy individuals on the basis of scores obtained from a social adjustment scale, an obstetric complications scale, and on family history of illness criteria (Cannon, et al., 1997). The results indicated that poor social development during a patients childhood years was often a precursor to the later development of a psychiatric illness. Stable, poor premorbid functioning, unmarked by a distinct decline, revealed the strongest association to schizophrenia onset. This reveals that positive cognition and social development were never achieved and completely absent within the premorbid period. Lower birth weight, sometimes as a result of obstetric complications, was correlated with lower scores on the Premorbid Adjustment Scale (PAS). The PAS, which measures adjustment based on social accessibility-isolation, peer relationships, scholastic performance, ability to function outside the nuclear family, and capacity to form intimate socio-sexual ties (Cannon-Spoor, et al., 1982), assesses functioning during four different life periods (childhood [up to 11 years], early adolescence [12-15 years], late adolescence [16-18 years], and adulthood [19 years and on]). Scores of the scale have been associated with SNP's within *DTNBPI* (Gornick, et al., 2005). Gornick, et al. tested fourteen SNP's of

DTNBPI amongst ninety-two dysbindin-positive patients diagnosed with child-onset schizophrenia. Four of these SNP's, P3762, P2215, P1763, and P3521, were significantly associated with low subcomponent and total PAS Scores: the latter also correlated with poorer social withdrawal and impaired peer relationships PAS scores.

Both cognitive deficits and premorbid indicators, such as a poor social development and low birth weight, have been linked with poor symptomatology in the prodromal period. Negative symptom severity, in particular, may be associated with such deterioration since it is often correlated with cognitive decline. Thus, current symptom severity may be influenced by a number of different pre-illness factors (*DTNBPI* haplotype status, cognitive impairment, premorbid variables), or a combination of them.

Based on prior research indicating the importance of premorbid indicators (including prenatal complications, learning disabilities, and developmental delays), their influence on current level of functioning, and genetic variations in *DTNBPI*, a retrospective chart review was conducted to determine which constituents of premorbid functioning are associated with both dysbindin-positive schizophrenia and measures of illness severity.

Methods

Subjects

For the past eight years, demographic, diagnostic, and treatment data on all patients participating in research studies at the Zucker Hillside Hospital in Glen Oaks, New York, have been recorded in a database. All subjects in the database had signed informed consent, and were assessed by a trained and expert-approved rater using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV) (First, et. al., 1997). Every module of the SCID is completed using the subject's report of past and

present psychiatric symptoms. Current and past inpatient records as well as collateral information from family members supplement the subject's report.

Eighty-nine Caucasian patients with a diagnosis of schizophrenia or schizoaffective disorder (SAD), including 45 dysbindin-positive patients and 44 dysbindin-negative patients matched according to age, sex, and age at onset, were included in the sample.

Negative Symptoms

Negative symptom scores were taken from ratings of three items, avolition, alogia, and affective flattening, within the SCID. The scores were rated on a continuous scale where 1=absent, 2=subthreshold, and 3=present. The total ratings thus reflect a lifetime history of negative symptoms.

Cognitive Functioning

Six different standardized cognitive tests were administered to all patients including the Wide Range Achievement Test- Third Edition- Reading Subtest (WRAT-3), the Wechsler Adult Intelligence Test-Revised (WAIS-R)- Digit Span, the Continuous Performance Test- Identical Pairs Version (CPT-I/P), the California Verbal Learning Test (CVLT)-Abridged, the Controlled Oral Word Association Test (COWAT), and the Trail Making Tests A&B. By examining all test scores rather than viewing cognitive domains, a total measure of cognitive functioning could be achieved. Using the unrotated first principal component analysis (PCA), which accounts for approximately 40% of the variance in scores on these various tests, the measure of general cognitive ability (*g*) was calculated (Carroll, 1997).

Family History

The Hillside Hospital Unit of Molecular Psychiatry Family History Questionnaire was administered to all patients. Information regarding maternal and paternal history in both first and second degree relatives was based upon the patient's report, available medical records, and, when available, reports of first degree relatives. Based on the resulting data, the patient group was dichotomized by family history negative (0) and family history positive (1). A patient was considered family history positive if any 1st or 2nd degree family member had a history of schizophrenia, bipolar disorder, major depression, alcoholism, or of psychotic symptoms.

Genetics

Genotyping was performed using MALDI-ToF mass spectrometry by means of the Sequenom system for the following SNP's: P1635, P1320, P1578, P1763, and P1765. Standards of Hardy-Weinberg Equilibrium (HWE) (Hill, 1974) were met at nearly all SNP loci. P1635 was found out of HWE in cases and controls and was thus excluded from analysis.

Results

From the original sample of eighty-nine patients identified, twenty-one patients were included in the analyses for this report. Exclusion of the remaining patients was due to the lack of vital variables in their data. Patients were only included if their medical records yielded conclusive information regarding the presence or absence of illness through familial traces, prenatal complications, and childhood delays.

There were no significant differences between carriers and non-carriers, respectively, in sex (77.5% male versus 22.5% female), age (mean=41.21 years,

SD=10.1, versus mean=40.20 years, SD 10.5), or age at onset of schizophrenia (mean=21.04 years, SD=6.40, versus mean=21.06 years, SD=4.84). This demographic data is illustrated in Table 1.

Table 1.			
Demographics			
<u>Variables</u>	<u>Carriers</u>	<u>Non-carriers</u>	<u>Statistics</u>
Age	Mean= 41.21 (S.D.= 10.105) N= 34	Mean= 40.20 (S.D.= 10.451) N= 35	t= -.406 (p<.686)
Age at Onset	Mean= 21.04 (S.D.= 6.403) N= 34	Mean= 21.06 (S.D.= 4.844) N= 35	t= .011 (p<.992)
Sex (% female)	Female= 10 Male= 24	Female= 13 Male= 22	X ² =.464 (p<.336)

A stepwise multiple regression analysis was conducted to assess the contribution of variables including first degree family history of illness, presence of the *DTNBP1* risk haplotype, presence of childhood problems (including developmental delays, learning disabilities, and prenatal complications), and a measure of general cognitive ability (*g*) on the overall negative symptom score. This analysis revealed that the model which best accounted for variation in negative symptom severity included first degree family history of illness and presence of the *DTNBP1* risk haplotype ($F=4.208$, $df=20$, $p<0.032$). Presence of childhood problems and scores of general cognitive ability did not significantly contribute to severity of negative symptoms, and were thus excluded from further analyses.

Post-hoc univariate analysis of variance (ANOVA) was conducted to assess the effect of the *DTNBP1* risk haplotype and family history of illness on overall negative symptom severity. This analysis indicated a significant effect of both the *DTNBP1* risk haplotype ($F=6.918$, $p<.011$) and family history of illness ($F=4.964$, $p<.029$). Specifically, carriers of the *DTNBP1* risk haplotype had a mean negative symptom score of 5.849 ($s.d=0.403$) vs. non-carriers who had a mean of 4.371 ($s.d=0.392$). Patients with

a positive family history of illness had a mean negative symptom score of 4.484 (s.d=0.275) vs. patients with a negative family history of illness who had a mean of 5.736 (s.d=0.490). These data are illustrated in Figures 1 and 2, respectively. Further, these analyses also indicated a significant interaction between the *DTNBP1* status and family history of illness ($F=7.606$, $p<.007$), suggesting that *DTNBP1* may only increase risk for severe negative symptoms in the context of a lack of family history of illness. Specifically, carriers of the *DTNBP1* risk haplotype with a positive family history had a mean negative symptom score of 4.4483 (s.d=1.95642) while carriers with a negative family history had a mean score of 7.2500 (s.d=2.25198). Conversely, non-carriers with a positive family history had a mean score of 4.5200 (s.d=2.02320) while non-carriers with a negative family history had a mean score of 4.2222 (s.d=1.98606). This data is illustrated in Figure 3.

Figure 1- Association of the *DTNBP1* CTCTAC risk haplotype with negative symptom severity. The x-axis represents the absence or presence of the haplotype. The y-axis represents the accumulation of negative symptom scores taken from a combination of avolition, alogia, and affective flattening scale values. The presence of the polymorphisms indicates a severe increase in symptomatology. The overall effect of the genotype is significant at $P=0.011$. (Bars represent standard error of the mean.)
*Significant at $p<0.05$

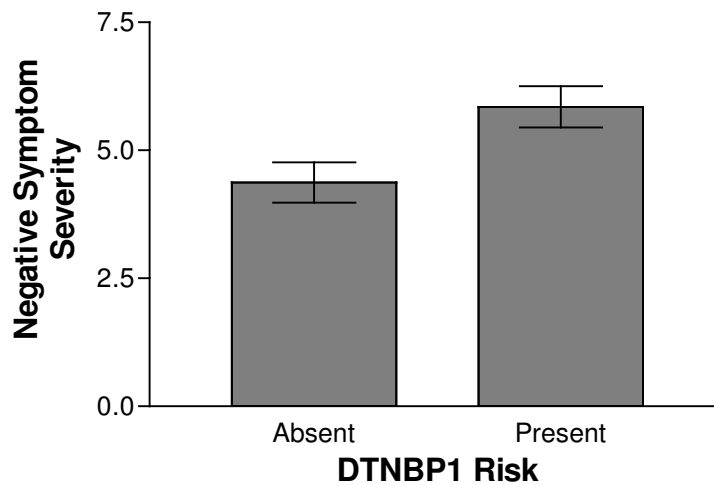


Figure 2- Association of a positive family history of illness with negative symptom severity. The x-axis represents the absence or presence of a familial history of illness loading. The y-axis represents the accumulation of negative symptom scores taken from a combination of avolition, alogia, and affective flattening scale values. The presence of a positive family history indicates a severe decrease in symptomatology. The overall effect of the family history is significant at $P=0.029$. (Bars represent standard error of the mean.)

*Significant at $p<0.05$

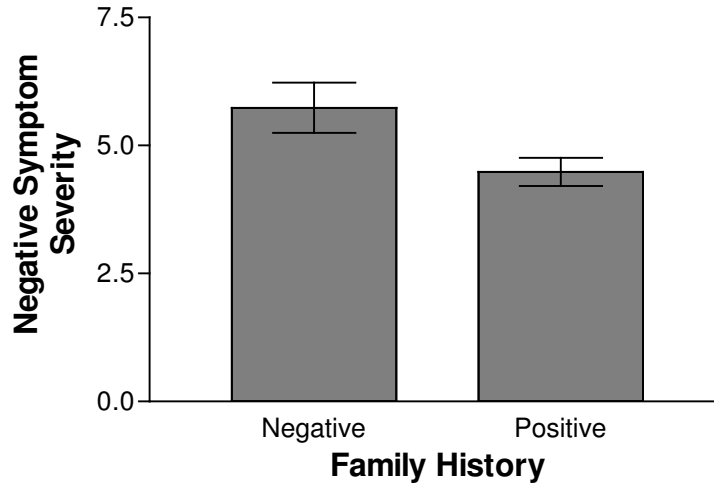
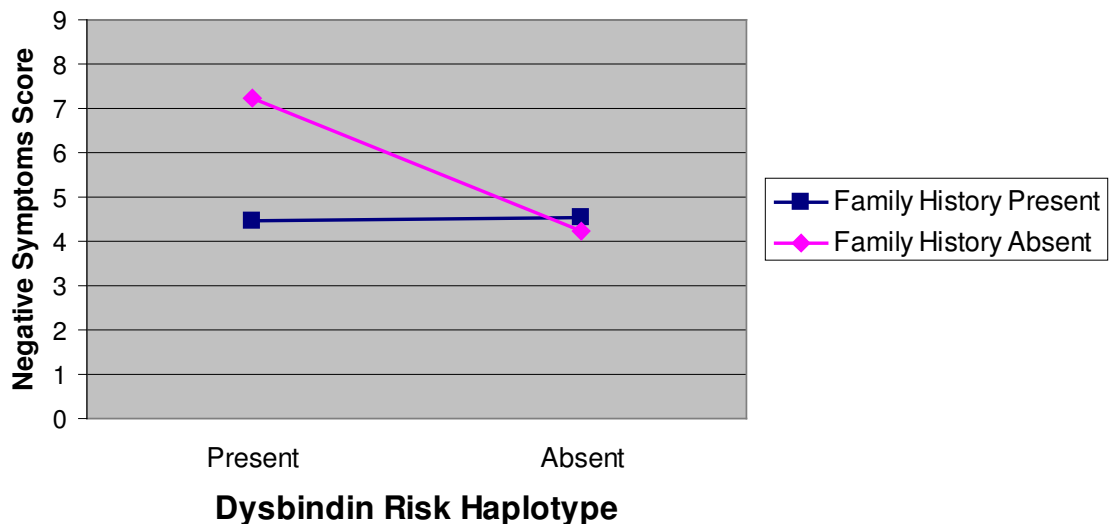


Figure 3- Relationship between the dysbindin risk haplotype and a positive family history of illness. The x-axis represents the absence or presence of the *DTNBP1* CTCTAC risk haplotype. The y-axis represents the accumulation of negative symptom scores taken from a combination of avolition, alogia, and affective flattening scale values. The graphed lines represent both the presence and absence of a familial history of illness loading. The overall effect of the combination of both family history and the risk haplotype is significant at $P=0.032$.

*Significant at $p<0.05$

Interaction Between Positive Family History and DTNBP1 Haplotype Status



Discussion

A significant association was found between the severity of negative symptoms on the SCID amongst schizophrenia patients and presence of the CTCTAC *DTNBPI* risk haplotype. When a stepwise multiple regression analysis was conducted according to negative symptomatology in the sample, the variables found to influence symptom severity included first degree family history of illness and presence of the *DTNBPI* risk haplotype.

In contrast to the original hypothesis, post-hoc tests revealed a novel finding that the presence of a positive family history was associated with a lower negative symptom score (*Figure 2*). This result indicates that while the *DTNBPI* risk haplotype and family history each individually plays a role in the course of negative symptomatology, their interaction is more predictive of symptom scores. A patient whose family members have had a mental disorder may possess gene loadings aside from the *DTNBPI* risk haplotype that influence illness response. These hereditary factors are bound to increase the risk of onset of an illness. The *DTNBPI* genotype, in this case, does not play a significant role in the severity of negative symptoms. Conversely, a patient whose family has had no encounters with mental disorders may not possess a significant genetic loading, and the introduction of a new mutation could be the introduction of a hereditary disorder. Thus, the presence of the *DTNBPI* genotype does not contribute to the severity of negative symptom scores in sporadic cases.

There are various limitations to this study that reinforce the benefits of a replication study. First, information regarding negative symptoms and family history may not be the most reliable sources. Although negative symptomatology was derived

from the SCID, which assessed a history of symptoms, there are other sources like the Scale for the Assessment of Negative Symptoms that may provide a clearer evaluation of these scores. Information regarding family history may also not be from the most accurate source as it comes from the Family History Questionnaire, for which the patient relays information from his or her memory. Second, only one haplotype within *DTNBPI* was analyzed. There are other *DTNBPI* risk haplotypes that have previously been associated with schizophrenia and may be important. In addition to utilizing additional polymorphisms and even genotyping information of other schizophrenia-susceptibility loci, further investigation should alter the sample group. This sample included twelve dysbindin-positive patients and fourteen dysbindin-negative patients with a positive family history of illness. A larger sample is needed. With the inclusion of more patients, all neurocognitive measures could have been used to examine measures within each individual cognitive domain. Childhood problems, as well, could have been examined individually with their increased prevalence as opposed to reviewing them as a combined unit. In addition, the nature of a retrospective study as opposed to a prospective study limits the ability of researchers to track a patient's course of illness rather than examine it afterwards.

In conclusion, negative symptom severity in schizophrenia is influenced by the presence of a first degree family history of illness as well as the presence of the CTCTAC *DTNBPI* risk haplotype. Scores on the measure of general cognitive ability (*g*) and the presence of childhood indicators, such as developmental delays, learning disabilities, and prenatal complications, did not predict the severity of symptoms. While further investigation is necessary, these novel findings validate the role that hereditary factors

play in the course of schizophrenia. In particular, *DTNBPI* remains a valuable source for the roots of the illness.

References

- Benson MA, Newey SE, Martin-Rendon E, Hawkes R, Blake DJ. (2001). Dysbindin, a novel coiled-coil-containing protein that interacts with the dystrobrevins in muscle and brain. *Journal of Biological Chemistry*, **276**, 24232–41.
- Bowie CR, Harvey PD. (2005). Cognition in schizophrenia: impairments, determinants, and functional importance. *The Psychiatric Clinics of North America*, **28(3)**, 613-33, 626.
- Bray NJ, Preece A, Williams NM, Moskvina V, Buckland PR, Owen MJ, O'Donovan MC. (2005). Haplotypes at the dystrobrevin binding protein 1 (*DTNBPI*) gene locus mediate risk for schizophrenia through reduced *DTNBPI* expression. *Human Molecular Genetics*, **14**, 1947-54.
- Burdick KE, Lencz T, Funke B, Finn CT, Szeszko PR, Kane JM, Kucherlapati R, Malhotra AK. (2006) Genetic variation in *DTNBPI* influences general cognitive ability. *Human Molecular Genetics*, **10**, 1563-68.
- Cannon M, Jones P, Gilvarry C, Rifkin L, McKenzie K, Foerster A, Murray RM. (1997). Premorbid Social Functioning in Schizophrenia and Bipolar Disorder: Similarities and Differences. *American Journal of Psychiatry*, **154**, 1544-50.
- Cannon-Spoor E, Potkin SG, Wyatt RJ. (1982) Measurement of Premorbid Adjustment in Chronic Schizophrenia. *Schizophrenia Bulletin*, **8**, 470-84.
- Carroll JB. (1997) Psychometrics, Intelligence, and Public Policy. *Intelligence*, **24**, 25-52.
- DeRosse P, Funke B, Burdick KE, Lencz T, Ekholm JM, Kane JM, Kucherlapati R, Malhotra AK. (2006) Dysbindin Genotype and Negative Symptoms in Schizophrenia. *American Journal of Psychiatry*, **163**, 532-34.
- Fanous AH, Van Den Oord EJ, Riley BP, Aggen SH, Neale MC, O'Neill FA, Walsh D, Kendler KS. (2005). Relationship between a high-risk haplotype in the *DTNBPI* (dysbindin) gene and clinical features of schizophrenia. *American Journal of Psychiatry*, **162**, 1824-32.
- First MB, Spitzer R, Gibbon M, Williams J. (1997) SCID-I: Structured Clinical Interview DSM-IV. *American Psychiatric Press*, New York, NY.
- Funke B, Finn CT, Plocik AM, Lake S, DeRosse P, Kane JM, Kucherlapati R, Malhotra AK. (2004) Association of the *DTNBPI* locus with schizophrenia in a US population. *American Journal of Human Genetics*, **75**, 91–898.
- Gornick MC, Addington AM, Sporn A, Gogtay N, Greenstein D, Lenane M, Gochman P, Ordonez A, Balkissoon R, Vakkalanka R, Weinberger DR, Rapoport JL, Straub RE. (2005) Dysbindin (*DTNBPI*, 6p22.3) Is Associated With Childhood-Onset Psychosis and Endophenotypes Measured By the Premorbid Adjustment Scale (PAS). *Journal of Autism and Developmental Disorders*, **35(6)**, 831-38.
- Hallmayer JF, Kalaydjieva L, Badcock J, Dragovic M, Howell S, Michie PT, Rock D, Vile D, Williams R, Corder EH, Hollingsworth K, Jablensky A. (2005). Genetic evidence for a distinct subtype of schizophrenia characterized by pervasive cognitive deficit. *American Journal of Human Genetics*, **77**, 468-76.

- Hill WG. (1974). Estimation of linkage disequilibrium in randomly mating populations. *Heredity*, **33**, 229-39.
- Kendler, K. (2004) Schizophrenia Genetics and Dysbindin: A corner Turned? *American Journal of Psychiatry*, **161**, 1533-36.
- Mortimer A, Spence S. (2003) Managing Negative Symptoms of Schizophrenia. *American Journal of Psychiatry*, **160**, 807.
- Plomin R. (1999). Genetics and general cognitive ability. *Nature*, **402**, C25–C29.
- Plomin R, Spinath FM. (2004). Intelligence: genetics, genes, and genomics. *Journal of Personal Social Psychology*, **86**, 112-29.
- Posthuma D, Luciano M, Geus EJ, Wright MJ, Slagboom PE, Montgomery GW, Boomsma DI, Martin NG. (2005). A genomewide scan for intelligence identifies quantitative trait loci on 2q and 6p. *American Journal of Human Genetics*, **77**, 318-26.
- Schwab SG, Knapp M, Mondabon S, Hallmayer J, Borrmann-Hassenbach M, Albus M, Lerer B, Rietschel M, Trixler M, Maier W, Wildenauer DB. (2003) 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. *American Journal of Human Genetics*, **72**, 185–90.
- Straub RE, MacLean CJ, O'Neill FA, Burke J, Murphy B, Duke F, Shinkwin R, Webb BT, Zhang J, Walsh D. (1995) A potential vulnerability locus for schizophrenia on chromosome 6p24-22: evidence for genetic heterogeneity. *Natural Genetics*, **11**, 287–93.
- 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. (2002). Genetic variation in the 6p22.3 gene *DTNBP1*, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. *American Journal of Human Genetics*, **71**, 337-48.
- Talbot K, Eidem WL, Tinsley CL, Benson MA, Thompson EW, Smith RJ, Hahn CG, Siegel SJ, Trojanowski JQ, Gur RE, Blake DJ, Arnold SE. (2004) Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. *The Journal of Clinical Investigation*, **113**, 1353–63.
- Weickert CS, Straub RE, McClintock BW, Matsumoto M, Hashimoto R, Hyde TM, Herman MM, Weinberger DR, Kleinman JE. (2004). Human dysbindin (*DTNBP1*) gene expression in normal brain and in schizophrenic prefrontal cortex and midbrain. *Archives of General Psychiatry*, **61**, 544–55.
- 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. (2004). Identification in 2 independent samples of a novel schizophrenia risk haplotype of the dystrobrevin binding protein gene (*DTNBP1*). *Archives of General Psychiatry*, **61**, 336-44.