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DTNBP1 Genotype Influences Cognitive Decline in Schizophrenia

Katherine E. Burdick, PhD[a,b], **Terry E. Goldberg, PhD**[a], **Birgit Funke, PhD**[c], **John A. Bates, PhD**[a], **Todd Lencz, PhD**[a,b], **Raju Kucherlapati, PhD**[c], and **Anil K. Malhotra, MD**[a,b]

a *Division of Psychiatry Research, The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, Glen Oaks, NY*

b *Albert Einstein College of Medicine*

c *Harvard Partners Center for Genetics and Genomics, Boston, MA*

Abstract

Objective—Intellectual decline is common in schizophrenia and predicts functional outcome. While many patients undergo intellectual decline that typically predates the onset of symptoms, few studies have investigated the underlying mechanism through which this occurs. The current study assessed the relationship between intellectual decline in schizophrenia and genetic variation in dysbindin-1 (*DTNBP1*).

Methods—We assessed cognitive decline in 183 Caucasian patients with schizophrenia using a proxy measure of premorbid IQ with which current general cognitive ability (*g)* was compared. We then tested for a relationship between the risk haplotype identified in previous work (CTCTAC) and intellectual decline.

Results—We found that carriers of the CTCTAC haplotype, demonstrated a significantly greater decline in IQ as compared with non-carriers (p=0.05).

Conclusions—These data suggest that *DTNBP1* influences the severity of intellectual decline in schizophrenia and may represent one underlying cause for heterogeneity in cognitive course.

Keywords

dysbindin; schizophrenia; cognitive decline; genetics

1.1 INTRODUCTION

Substantial evidence suggests that a large proportion of patients with schizophrenia undergo a decline in intellectual functioning; however, there is considerable inter-individual variation in the degree of decline. Studies that have investigated intellectual functioning prior to the onset of schizophrenia and after illness onset, indicate that approximately 40–50% of patients are "deteriorating", with an IQ decline of ≥ 10 points from premorbid IQ, while another 50% of patients do not demonstrate significant intellectual decline (Reichenberg et al. 2005; Weickert et al. 2000).

Correspondence Katherine E. Burdick, PhD, The Zucker Hillside Hospital, North-Shore-Long Island Jewish Health System, 75-59 263rd Street, Glen Oaks, NY 11004. Telephone (718) 470-8167, Fax: (718) 343-1659, Email: kburdick@lij.edu.

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These data also suggest that many patients' intellectual functioning is impaired prior to the onset of illness (Reichenberg et al. 2005, 2002; Fuller et al. 2002; Weickert et al. 2000). Reichenberg et al. (2005) recently reported that a majority of healthy adolescents who later manifest schizophrenia undergo a significant intellectual decline prior to the onset of psychotic symptoms. Intellectual decline, defined as a significantly lower than expected IQ at age 17, was associated with an increased risk for developing schizophrenia (Reichenberg et al. 2005). Subsequent to the initial episode (Bilder et al. 2006), cognitive performance, although impaired, appears to remain relatively stable in most patients, over short (2-year) and long (5-year and 10-year) term follow-up (Burdick et al. 2006a; Heaton et al. 2001). Given the early presence of decline and its stability over time, it is likely that genetic influences play a role in determining the severity of the decline, yet to date there have been no studies to identify specific genes that may differentiate these heterogeneous cognitive profiles.

Recently, however, a growing body of evidence suggests that the gene coding for dysbindin-1 (*DTNBP1*), initially identified by Straub and colleagues (2002), might influence intellectual decline in schizophrenia. First, *DTNBP1* has been shown to influence risk for schizophrenia in several genetic linkage and association studies (for review see Norton et al. 2006), although not all studies have reported positive results. Second, post-mortem evidence suggests that *DTNBP1* is expressed in regions of the brain that are critical to cognitive function and that its expression is reduced in hippocampus and prefrontal cortex in patients with schizophrenia (Weickert et al. 2004). Third, knockdown of endogenous dysbindin in primary cortical neuron culture results in decreased pre-synaptic protein expression and decreased release of glutamate (Numakawa et al. 2004), a key neurotransmitter thought to underlie cognitive dysfunction in schizophrenia. Finally, recent data from our group suggests that a schizophrenia risk haplotype in *DTNBP1* (Funke et al. 2004) is associated with decreased general cognitive ability (*g*) in patients with schizophrenia and healthy volunteers (Burdick et al. 2006b). In this study group, we also have data on premorbid intellectual function and we have now assessed the effects of this 6-locus *DTNBP1* risk haplotype (CTCTAC) on premorbid versus post-illness onset intelligence in 183 patients with schizophrenia to test the hypothesis that *DTNBP1* influences intellectual decline in schizophrenia.

1.2 EXPERIMENTAL/MATERIALS AND METHODS

The sample consisted of 183 unrelated Caucasian patients with schizophrenia or schizoaffective disorder who were administered a battery of standardized cognitive measures comprised of the Wechsler Adult Intelligence Test-Revised (WAIS-R)-Digit Span; Continuous Performance Test-Identical Pairs Version (CPT-I/P); California Verbal Learning Test (CVLT)-Abridged; Controlled Oral Word Association Test (COWAT), and Trail Making Tests A&B. Subjects were included if they were age 25 to 64 and had an estimated premorbid IQ >70 and represent a subset of the sample reported on in Burdick et al. 2006a.

Genotyping and haplotype procedures are described in detail elsewhere (Funke et al. 2004; Burdick et al. 2006a). Briefly, six single nucleotide polymorphisms [P1583-(rs909706), P1578-(rs1018381), P1763-(rs2619522), P1320-(rs760761), P1765-(rs2619528), and P1325-(rs1011313)] were genotyped and met criteria for Hardy-Weinberg equilibrium. We utilized the SNPHAP program (Department of Medical Genetics, Cambridge Institute for Medical Research, Addenbrooke's Hospital, Cambridge, U.K) for estimating haplotype frequencies, which uses an estimation method algorithm to calculate maximum likelihood estimates of haplotype frequencies given genotypes which do not specify phase. We included subjects whose haplotypes could be assigned with a confidence of $\geq 95\%$. We focused our analyses on the single risk haplotype (CTCTAC) for schizophrenia from our previous work (Funke et al. 2004).

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When longitudinal data are not available, an alternative approach to measure intellectual decline is to estimate premorbid IQ in patients with schizophrenia by using tests of reading skill. We assessed cognitive decline using the Wide Range Achievement Test-Third Edition-Reading Subtest (WRAT-3) as a proxy for premorbid IQ. WRAT-3 is a test that assesses single word reading skill which, like command of general knowledge and vocabulary, is particularly resistant to the effects of deterioration associated with brain disease and is considered an estimate of pre-morbid IQ in patient populations (Kremen et al. 1996; Goldberg et al. 1995).

As a measure of current IQ, with which WRAT-3 scores were compared, "general cognitive ability", or (*g)*, was calculated as the first component of an unrotated principal components analysis utilizing all of the cognitive tests administered, except the WRAT-3. All cognitive variable data were transformed to standardized z-scores and missing values were replaced by the mean of the group. No case with more than two missing values was retained in the sample. A single factor model was produced (extracted variables with eigenvalues of > 1.0 using the regression method). This first unrotated factor explained 48.5% of the variance and represented our generalized cognitive ability factor. Each of the individual measures loaded onto the first factor with covariance of > 0.61. A detailed description of the PCA methods used to derive *g* is provided in Burdick et al. (2006a).

For exploratory purposes, we also characterized our patients, consistent with previous methods (Reichenberg et al. 2005; Weickert et al. 2000), as "deteriorating" if they experienced an IQ decline of ≥ 10 points and as "stable" if they did not meet this threshold.

1.2.1 Statistical Analyses

All scores were transformed to standard scores for uniformity in comparing across measures. Consistent with methodology used in Kremen et al. (2001) we measured putative decline from premorbid IQ by using a regression approach. This method is preferable to using raw score differences because the premorbid-current discrepancy may not be equivalent at all IQ levels. This was done by regressing *g* on WRAT-3 in our healthy controls (n=126) and using the regression model to generate standardized scores, representing predicted IQ in the schizophrenia group. A residual score (observed minus predicted) reflected whether a subject's current IQ was above or below their premorbid IQ. Thus, the putative IQ change described below is actually the discrepancy between current IQ, as measured by *g*, and an *expected* IQ based on a predicted score (Reichenberg et al. 2005). Hence, data are presented as residual scores as opposed to raw scores.

Univariate analysis of variance (ANOVA) was used with haplotype group as the between-subjects factor and the residual score reflecting decline as the dependent variable. Haplotype groups were defined as carriers of the CTCTAC risk haplotype (with one or two copies; n=35) versus non-carriers of CTCTAC (no copies; n=148); heterozygote and homozygote carriers were merged due to the low frequency of homozygotes (n=4).

1.3 RESULTS

We found that patients with schizophrenia who carry the CTCTAC risk haplotype demonstrated a significantly greater decline in IQ (residual mean change=13.5±13.6) as compared with patients who do not carry the risk haplotype (residual mean change=8.7±12.4) (F=4.00; df=1, 182; p=0.05; Figure 1). Effect size calculations indicated that *DTNBP1* genotype accounted for 2.2% of the variance in intellectual decline.

Haplotype groups did not differ on demographic or illness characteristics: Carrier vs. non-carrier: (Age=43.7±8.7 years vs. 40.7±8.7 years; Sex 40.0% female vs. 35.8% female; Education=13.0±2.3 years vs. 12.9±3.5 years; Age of onset=18.4±5.7 years vs. 18.4±5.8 years;

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Global Assessment of Function-GAF score=38.7±12.6 vs. 40.8±13.9; ; Duration of illness 26.5 ± 9.0 years vs. 22.4± 10.6 years; all p-values > 0.05). Consistent with previous reports (1, 2), 45.4% of patients demonstrated intellectual decline of at least ten points were characterized as "deteriorating". In the group of deteriorating patients, the risk haplotype had a frequency of 24%, as compared with a frequency of only 15% in the non-deteriorating group, but this difference did not reach statistical significance (Chi^2=2.43; p=0.12).

1.4 DISCUSSION

General intellectual decline is an important feature of schizophrenia and has been demonstrated to predict both functional outcome and variance in other more specific cognitive measures (Weickert et al. 2000). Here we show a significant effect of a *DTNBP1* risk haplotype (CTCTAC) on IQ decline in patients with schizophrenia. CTCTAC carriers demonstrated a significantly greater decline in IQ (13.5 units) as compared with non-carriers (8.7 units), as measured via proxy measurements of premorbid IQ and current IQ. Among those patients who were characterized as deteriorating, the risk haplotype had a frequency of 24%, as compared with a frequency of only 15% in the non-deteriorating group. These data are consistent with a study by Williams et al. (2004) in which a 3-locus haplotype in *DTNBP1* was associated with educational attainment in patients with schizophrenia and in healthy controls. These data also suggest that different mechanisms may play a role in cognitive function in schizophrenia patients prior to the onset of illness versus healthy controls, as our previous study found an effect of *DTNBP1* on general cognitive ability in healthy controls (Burdick et al. 2006a).

The mechanism underlying the effect of *DTNBP1* genotype on intellectual decline is unknown, although its broad distribution in brain, along with reported reductions of *DTNBP1* expression in regions critical to cognitive function (Weickert et al.2004), suggests that intellectual decline may be related to decreased *DTNBP1* expression. This is supported by preliminary data from a knockdown model demonstrating that reduced *DTNBP1* expression results in dysfunction within the glutamatergic system (Numakawa et al. 2004), a system believed to be related to cognitive function and disrupted in schizophrenia.

This study has several limitations including a relatively small sample of CTCTAC carriers due to the low frequency of the risk haplotype. This likely impacted the statistical power, resulting in significant, but modest p-value. In addition, we utilized a proxy measure for estimating premorbid IQ, as opposed to measuring decline via a longitudinal design. While longitudinal studies that measure IQ prior to disease onset are preferable, they are difficult to conduct given the low prevalence of the disease and the difficulties inherent in long-term follow-up of individuals prior to the onset of illness. Finally, although our data suggest that *DTNBP1* genotype has an effect on intellectual decline, to date, a number of overlapping but not identical *DTNBP1* risk haplotypes have been identified but no functional variant has been found within the gene.

In conclusion, we report an association between *DTNBP1* and intellectual decline in patients with schizophrenia. These data provide evidence for an underlying genetic vulnerability that may influence the developmental trajectory of schizophrenia, at least with regard to cognitive symptoms.

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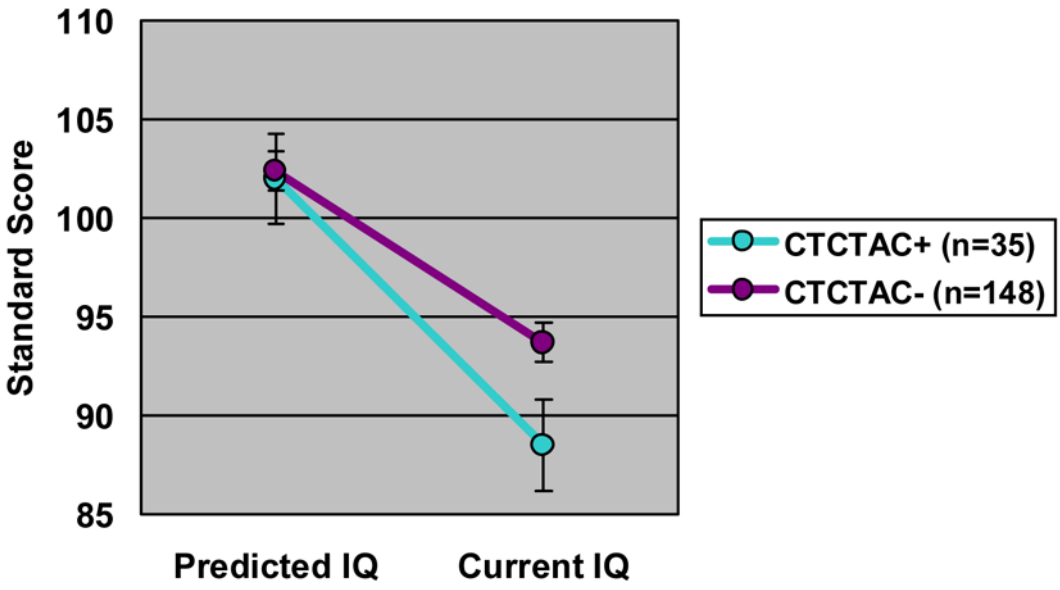

[a]Main effect of *DTNBP1* Genotype (F=4.0, df=1,182, p=0.05). Error bars represent Standard Error of the Mean (SEM).

Figure 1. Intellectual Decline in Patients with Schizophrenia by *DTNBP1* Genotype

Carriers of the CTCTAC risk haplotype demonstrate a greater intellectual decline than non-carriers. The data represent residual scores (observed minus predicted IQ) and are presented on the y-axis as Standard Scores (with a mean of 100 and a standard deviation of 15). The x-axis illustrates change from predicted IQ to current IQ in carriers versus non-carriers.