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Genetic variation in *DTNBP1* influences general cognitive ability

Katherine E. Burdick[1,2,*], Todd Lencz[1,2], Birgit Funke[3], Christine T. Finn[3], Philip R. Szeszko[1,2], John M. Kane[1,2], Raju Kucherlapati[3] and Anil K. Malhotra[1,2]

[1]Department of Psychiatry Research, The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System and [2]Department of Psychiatry, Albert Einstein College of Medicine, Glen Oaks, NY, USA and [3]Harvard Partners Center for Genetics and Genomics, Boston, MA, USA

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Human intelligence is a trait that is known to be significantly influenced by genetic factors, and recent linkage data provide positional evidence to suggest that a region on chromosome 6p, previously associated with schizophrenia, may be linked to variation in intelligence. The gene for dysbindin-1 (*DTNBP1*) is located at 6p and has also been implicated in schizophrenia, a neuropsychiatric disorder characterized by cognitive dysfunction. We report an association between *DTNBP1* genotype and general cognitive ability (*g*) in two independent cohorts, including 213 patients with schizophrenia or schizo-affective disorder and 126 healthy volunteers. These data suggest that *DTNBP1* genetic variation influences human intelligence.

INTRODUCTION

A robust body of evidence suggests that cognitive abilities, particularly intelligence, are significantly influenced by genetic factors (1). The psychometric definition of intelligence was first described in the early 20th century by Charles Spearman and measures a ‘general cognitive ability’ (Spearman’s *g*), which is the product of an unrotated first principal component analysis (PCA) score, accounting for ~40% of the variance in performance on diverse cognitive measures (2). The concept of *g* is widely accepted as a measure of intelligence (3,4) and is based on the significant covariance, or phenotypic overlap, of a number of different cognitive processes, such as memory, spatial ability and verbal ability (5). In other words, an individual who performs well on a measure of spatial ability is also likely to perform well on a range of other cognitive tasks, with a large proportion of variation in ability being accounted for by *g*.

Data from more than 8000 parent–offspring pairs, 25 000 sibling pairs, 10 000 twin pairs and adoption studies provide evidence that genetic factors play a substantial role in the variation of *g* (6), with heritability estimates ranging from 40 to 80%. This suggests that there are genetically influenced mechanisms that affect performance across a number of diverse cognitive measures. That is, a gene that influences working memory is also very likely to be associated with other cognitive abilities (i.e. processing speed) (7–9). Given the significant overlap of the phenotypic properties of cognition and the underlying genetic overlap of independent cognitive abilities, it has been suggested that *g*, despite its putative phenotypic complexity, can be considered an ideal target for molecular genetic studies.

Two recent linkage studies have provided converging positional evidence implicating a region on chromosome 6p in general cognitive abilities in both healthy subjects (10) and patients with schizophrenia (11). Posthuma *et al.* (10) recently reported a genome-wide scan identifying two chromosomal regions that demonstrate evidence of linkage for intelligence. In 634 sibling pairs derived from two unselected samples (475 sibling pairs from Australian families, 159 sibling pairs from Dutch families), model-free multipoint linkage analysis revealed strongly suggestive linkage at 6p25.3–22.3 for full-scale IQ (LOD score 3.20) and for verbal IQ (LOD score 2.33). This region overlaps with regions implicated in dyslexia, reading disability (12) and schizophrenia (13). Hallmayer *et al.* (11) reported that the linkage of schizophrenia to this region was specific to a subset of patients who were characterized by general cognitive deficit.

*To whom correspondence should be addressed at: Department of Psychiatry Research, The Zucker Hillside Hospital, North-Shore-Long Island Jewish Health System, 75-59 263rd Street, Albert Einstein College of Medicine, Glen Oaks, NY 11004, USA. Tel: +1 7184708167; Fax: +1 7183431659; Email: kburdick@lij.edu

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Table 1. Sample characteristics of subjects with and without the *DTNBP1* CTCTAC risk haplotype

Sample characteristic	Healthy volunteers		Schizophrenia patients		
	Carriers ($n = 15$)	Non-carriers ($n = 111$)	Carriers ($n = 39$)	Non-carriers ($n = 174$)	Statistic (*P*-value)
Age	54.7 (14.1)	50.7 (16.1)	41.7 (10.5)	37.9 (10.6)	−1.17 (0.24)
Sex (% female)	86.7	57.6	41.0	31.6	$X^2 = 2.6$ (0.11)
Education	15.7 (2.7)	16.1 (2.4)	13.0 (2.2)	12.8 (3.2)	1.16 (0.25)
Age of onset	—	—	18.0 (5.4)	18.1 (5.4)	0.13 (0.89)
GAF	—	—	38.2 (12.4)	41.1 (16.1)	0.99 (0.32)

The gene for dysbindin-1 (*DTNBP1*) is located at 6p22.3 and is a strong candidate to explain these linkage results. Although the specific role of *DTNBP1* in the central nervous system is unknown, dysbindin-1 is expressed widely in the brain, including regions in the frontal cortex, temporal cortex, hippocampus, caudate, putamen, nucleus accumbens, amygdala, thalamus and midbrain (14). Moreover, *DTNBP1* is demonstrated to influence risk for schizophrenia, a neuropsychiatric disorder characterized by cognitive impairment (15). Initial linkage of schizophrenia to this region was reported by Straub *et al.* (16), with subsequent demonstration of significant association of several variants in the gene that encodes for dysbindin at chromosome 6p22.3 (17). Several studies in different populations have been reported since and most have confirmed an association of schizophrenia with *DTNBP1* (18–24).

Recent work by our group (25) supports an association of *DTNBP1* with schizophrenia. In a study comprising 524 patients with schizophrenia or schizo-affective disorder and 573 healthy volunteers, we identified a six-locus haplotype (CTCTAC) that was significantly over-represented in the Caucasian patients when compared with Caucasian healthy volunteers ($P = 0.005$). The minor alleles of three individual SNPs [P1578-(rs1018381), P1763-(rs2619522) and P1765-(rs2619528)] were also significantly over-represented in patients (25). These studies, as well as reports of reductions in *DTNBP1* gene and protein expression in dorsolateral prefrontal cortex and hippocampal formation (26) in patients with schizophrenia, provide convergent evidence that *DTNBP1* is involved in schizophrenia. However, to date, there are no data that provide specific information on the relationship between *DTNBP1* genotype and cognition.

Therefore, as linkage and association data suggest that dysbindin may influence cognition, we have conducted a study specifically examining *DTNBP1* genotype in a large sample of subjects who were characterized for their cognitive performance. Subjects included patients with schizophrenia or schizo-affective disorder and healthy volunteers. We focussed our analyses on the phenotype of *g* because of its broader variance in schizophrenia, demonstrated heritability, and the recent positional evidence of linkage for intelligence to the chromosomal region containing *DTNBP1*. We hypothesized that carriers of the six-locus haplotype that we previously observed to be associated with increased risk for schizophrenia (25) would have lower *g* than subjects without the risk haplotype. We focused our primary analyses on this haplotype for several reasons: (i) This was the haplotype identified in our Caucasian population to increase risk for schizophrenia. (ii) This risk haplotype significantly overlaps with risk haplotypes observed by other groups (17,18,22). (iii) The frequency of the haplotype in schizophrenia patients and in healthy volunteers provided sufficient power to test its relationship to cognition in our data set.

RESULTS

Sample characteristics by genotype are presented in Table 1. The haplotype groups did not significantly differ on age, sex or education level. Patients did not differ by haplotype group on illness features including age at onset or global assessment of functioning (GAF).

Analysis of *g* revealed a significant overall effect of genotype, with poorer performance by carriers of the risk haplotype (mean $= -0.40 \pm 1.0$) when compared with non-carriers (mean $= 0.08 \pm 1.0$) ($F = 7.03$, df = 1, 338, $P = 0.008$). As expected, the effect of diagnostic type was significant ($F = 75.91$, df = 1, 338, $P < 0.001$); however, the diagnostic type by genotype interaction was not significant ($F = 0.02$, df = 1, 338, $P = 0.88$). Nonetheless, we assessed the effect of genotype on *g* in each group independently, with consistent results in each group. Healthy volunteers carrying the risk haplotype (mean $= 0.42 \pm 0.5$) performed significantly worse than non-carriers (mean $= 0.79 \pm 0.66$) ($F = 4.29$, df = 1, 125, $P = 0.040$) and schizophrenia patients carrying the risk haplotype (mean $= -0.72 \pm 1.0$) performed significantly worse than non-carriers (mean $= -0.38 \pm 0.9$) ($F = 4.50$, df = 1, 212, $P = 0.035$) (Fig. 1). An effect size estimate (partial η^2) suggests that genotype explains ~3% of the overall variance in *g* and was slightly larger in healthy volunteers (3.3%) than in patients with schizophrenia (2.1%). The absolute magnitude of the effect, however, is similar in both diagnostic groups (0.37 points in healthy volunteers and 0.34 points in patients with schizophrenia).

As age and sex are important factors related to cognitive performance, we ran secondary analyses to control for their effects and found that when co-varying for age, results remain significant ($P = 0.03$) and when entering sex as a fixed factor, again results remain significant ($P = 0.02$). In addition, owing to unequal sample sizes and variances between carriers and non-carriers, we ran a confirmatory analysis using a non-parametric approach, and results were slightly more significant (Mann–Whitney $U = 5754.0$, $P = 0.003$).

As we previously identified SNP 1578 to be a tagging SNP for the risk haplotype, we conducted analyses of this SNP using genotype and diagnostic type as fixed factors for analysis of *g*. Results revealed a significant effect of genotype on *g*

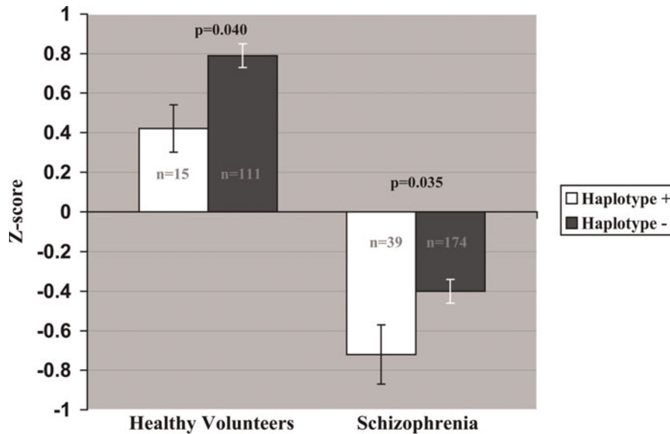

Figure 1. *DTNBP1* risk haplotype and general cognitive ability (*g*) in subjects with and without the *DTNBP1* CTCTAC risk haplotype. The *X*-axis represents subject type. The *Y*-axis represents the first factor from the PCA calculated for *g*. *Z*-scores are calculated using the standardized mean = 0 and SD = 1 from the healthy volunteer sample, such that lower values reflect worse performance. Error bars represent 95% confidence interval. The overall effect of genotype is significant at $P = 0.008$, and the subject type by genotype interaction is not significant.

($F = 5.09$, df = 1338, $P = 0.03$), with carriers of the risk allele performing significantly worse than non-carriers. There were no other significant results at any of the other five SNPs.

The complementary analysis, although not independent of the primary analyses, evaluating haplotype frequencies in the patient sample by comparing 'cognitive-deficit' versus 'cognitively spared' subgroups revealed that a significantly greater proportion of the cognitive-deficit patients carried the risk haplotype ($n = 17$, 28.3%) when compared with the cognitively spared subgroup of patients ($n = 22$, 14.4%) ($\chi^2 = 5.61$, df = 1, $P = 0.02$).

DISCUSSION

We evaluated the relationship between a *DTNBP1* haplotype (CTCTAC) previously observed by our group to be associated with schizophrenia (25) and a calculated measure of *g* (the first unrotated factor of a PCA with a number of diverse cognitive measures) in two independent samples including patients with schizophrenia and healthy volunteers and found that carriers of the risk haplotype had lower *g* when compared with non-carriers in both cohorts. The tagging SNP (SNP 1578) was also associated with *g* in both groups, whereas no other individual SNP was associated with neurocognition. Furthermore, when we characterized the patient sample by cognitive-deficit patients versus cognitively spared patients, we found that the cognitive-deficit patients were nearly twice as likely to carry the risk haplotype (27%) than the cognitively spared patients (15%). These data suggest that *DTNBP1* genotype plays a significant role in the inter-individual variation in *g*.

These data are convergent with Posthuma *et al.* (10), who recently provided evidence for linkage for intelligence to the chromosomal region containing *DTNBP1*. In addition, our results are consistent with the recent data of Hallmayer *et al.* (11), which suggested that the linkage to schizophrenia in the region of 6p may be driven by a cognitively impaired subgroup of patients characterized as such by a latent structure analysis. Furthermore, our data are consistent with hypothesized relationship between *DTNBP1* genotype and cognition, as suggested by Williams *et al.* (24), based on an association in their sample between level of education and a three-locus *DTNBP1* haplotype. These data suggest that *DTNBP1* may impart an increased risk for schizophrenia through its effects on the specific symptom domain of impaired cognition. However, the effect of *DTNBP1* on cognition may be only indirectly linked to its role in susceptibility to schizophrenia, as we observe a similar effect in healthy volunteers. Our data are also consistent with a number of recent associations between candidate genes and cognition in various populations, including catechol-*o*-methyl transferase (*COMT*) (7,8,27), disrupted in schizophrenia (*DISC1*) (28–30), succinate-semialdehyde dehydrogenase (*SSADH*) (31), apolipoprotein-E (*APOE*) (32) and *KLOTHO* (33).

The mechanism underlying the effect of *DTNBP1* genotype on cognitive performance is currently unclear, especially because it is broadly distributed throughout the central nervous system, including regions in the frontal cortex, temporal cortex, hippocampus, caudate, putamen, nucleus accumbens, amygdala, thalamus and midbrain (14). Dysbindin-1 binds to β-dystrobrevin, a component of the dystrophin glycoprotein complex (DPC) in the brain. Although the DPC is found at postsynaptic sites, several studies demonstrate presynaptic dysbindin expression in cerebellum and hippocampus (26,34). β-dystrobrevin interacts with proteins (dysbindin and muted) that are known subunits of biogenesis of lysosome-related organelles complex-1 (BLOC-1), raising the possibility that it may be involved in vesicle trafficking in non-muscle tissue (35). Li *et al.* (35) suggest that dysbindin may be independently part of both BLOC-1 and the DPC complex, with distinct vesicle trafficking functions for each (35).

Preliminary data suggest that *DTNBP1* genotype may impact upon the GABAergic and glutamatergic systems through reduced *DTNBP1* expression (36–38). For example, Numakawa *et al.* (37) presented a dysbindin knockdown model resulting in reduced glutamate release, thought to be caused by suppression of presynaptic proteins involved in intracellular vesicle trafficking. Interestingly, Bray *et al.* (36) demonstrated that the A allele of rs1047631, a SNP related to the schizophrenia risk haplotype in the Cardiff sample (24), was linked to reduced cortical expression of *DTNBP1* mRNA (36). Further, the T allele of the tagging SNP P1578, which was associated with lower *g* in the present study, is in complete linkage disequilibrium ($D' = 1$) with the A allele of rs1047631 in both the postmortem samples of Bray *et al.* and the CEPH (Utah residents with ancestry from Northern and Western Europe) samples of the HapMap Project (39). Thus, it is possible to speculate that the risk haplotype described in this report is associated with reduced dysbindin expression, resulting in decreased levels of glutamate release (24). It is important to emphasize, however, that no variant within *DTNBP1* has, as yet, provided direct evidence of functional effects; therefore, additional efforts will be needed to identify the putative functional locus.

In summary, we report an association between *DTNBP1* and *g* in two independent cohorts including patients with schizophrenia and healthy volunteers, suggesting that *DTNBP1* genotype influences variation in human cognitive ability and intelligence. Although these data suggest that *DTNBP1* may be a candidate gene for intelligence, *DTNBP1* genotype explained only a small proportion (3%) of the variance on this measure, supporting a model involving multiple genetic and environmental influences.

MATERIALS AND METHODS

Subjects

The study group included 213 unrelated Caucasian patients with schizophrenia or schizo-affective disorder and 126 unrelated Caucasian healthy volunteers. All subjects provided written informed consent to an Institutional Review Board of the North Shore-Long Island Jewish Health System (NSLIJHS)-approved protocol. Patients were recruited from the inpatient units of the Zucker Hillside Hospital (ZHH), a division of the NSLIJHS, in Glen Oaks, New York. Diagnosis was established through structured interview (structured clinical interview-DSM-IV; SCID-IV) (40) and confirmed by diagnostic consensus conference.

Healthy volunteers for the project were recruited from the general population. Advertisement was made by word of mouth, newspaper and internet advertisements and posted flyers. Prospective participants were administered the SCID-IV, non-patient edition (SCID-NP) specifically designed to assess healthy subjects.

In addition to the structured diagnostic interview, all potential subjects were screened to rule out any history of CNS trauma, neurological disorder or learning disability. A urine toxicology screen was also performed, and in the case of positive results, the subject was excluded. Healthy volunteers who identified a first-degree relative with an Axis I disorder were also excluded.

Cognitive measures

All subjects were administered a battery of standardized cognitive measures comprising the Wide Range Achievement Test-Third Edition-Reading Subtest (WRAT-3), 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 (41). Our primary-dependent measure was *g*, the first factor score derived from an unrotated principal components analysis, as previously described (2). Data reduction was achieved through factor analysis using principal components as the extraction method. All cognitive variable data were transformed to standardized *Z*-scores, using the healthy volunteers as the normative sample. *Z*-scores for all variables were entered, and a total of 14 missing values in the patient sample were replaced by the mean of the patient group. There were no missing values in the healthy sample. No case with more than one missing value was retained in the sample. PCA was conducted in each group separately. The factor structure was nearly identical in our healthy volunteers and patients with schizophrenia, with no factor loading difference greater than 0.15; therefore, the data were merged. The first unrotated factor explained 50% of the variance and represented our general cognitive ability factor. Each of the individual measures loaded onto the first factor with covariance of >0.55. Factor scores representing *g* are standardized using a *Z*-score scale with a mean of 0 and standard deviation of 1.

DNA procedures

Genomic DNA was extracted from venous blood samples using a standard protocol. Seven single nucleotide polymorphisms [P1583-(rs909706), P1578-(rs1018381), P1763-(rs2619522), P1320-(rs760761), P1765-(rs2619528), P1635-(rs3213207) and P1325-(rs1011313)] were genotyped using the MALDI-TOF mass spectrometry by the Sequenom system. However, only six of the markers met the criteria for Hardy–Weinberg equilibrium; hence, the seventh marker (P1635) was excluded from further analyses.

We utilized the SNPHAP program (David Clayton, University of Cambridge, UK) for estimating the haplotype frequencies, which uses an expectation-maximization algorithm to calculate maximum likelihood estimates of haplotype frequencies, given genotype measurements which do not specify phase. Any individual whose haplotypes could not be assigned with a confidence of 95% or greater were excluded from the final sample.

Statistical analyses

General cognitive ability (*g*) of subjects with at least one copy of the risk haplotype (CTCTAC) identified by Funke *et al.* (25) was compared with *g* of subjects having no copies of the haplotype, with independent univariate analysis of variance (ANOVA). Owing to the low frequency of homozygote risk haplotype carriers ($n = 7$), these subjects were grouped with heterozygote carriers for all analyses. Genotype and diagnostic type (patient versus healthy volunteer) were entered as fixed factors and alpha level was set at 0.05. Follow-up testing was conducted to assess the effect of genotype on *g* in each subject group independently.

In a complementary analysis of the patient sample, we assessed risk haplotype frequencies in a subgroup of patients defined as 'cognitive-deficit' (whose performance fell at least 1 SD below the mean *g*) ($n = 60$) and compared them with risk haplotype frequencies of a 'cognitively spared' subgroup of patients ($n = 153$) using χ^2.

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Conflict of Interest statement. None declared.

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