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Dysbindin (DTNBP1, 6p22.3) is Associated with Childhood-Onset Psychosis and Endophenotypes Measured by the Premorbid Adjustment Scale (PAS)

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Straub *et al.* (2002) recently identified the 6p22.3 gene dysbindin (DTNBP1) through positional cloning as a schizophrenia susceptibility gene. We studied a rare cohort of 102 children with onset of psychosis before age 13. Standardized ratings of early development, medication response, neuropsychological and cognitive performance, premorbid dysfunction and clinical follow-up were obtained. Fourteen SNPs were genotyped in the gene DTNBP1. Family-based pairwise and haplotype transmission disequilibrium test (TDT) analysis with the clinical phenotype, and quantitative transmission disequilibrium test (QTDT) explored endophenotype relationships. One SNP was associated with diagnosis (TDT $p = .01$). The QTDT analyses showed several significant relationships. Four adjacent SNPs were associated (p values = .0009–.003) with poor premorbid functioning. These findings support the hypothesis that this and other schizophrenia susceptibility genes contribute to early neurodevelopmental impairment.

KEY WORDS: Candidate gene; genetic association; transmission disequilibrium test; quantitative TDT; schizophrenia; DTNBP1; childhood onset.

Childhood-onset schizophrenia (COS), defined as onset of psychotic symptoms by age 12, is a rare and severe form of the disorder (Nicolson & Rapoport, 1999). Since 1990, patients with COS have been recruited nationally by the National Institute of Mental Health for clinical studies. COS appears clinically and neurobiologically continuous with the adult disorder (Nicolson & Rapoport, 1999), and evidence from medicine generally indicates that stratification by age of onset may serve to identify a more homogeneous patient group, less confounded by secondary effects of illness and with more salient genetic risk (Childs & Scriver, 1986; St George-Hyslop, 2000). Compared with adult onset patients, the COS population shows a higher rate of familial spectrum disorders (Asarnow *et al.*, 2001; Nicolson *et al.*, 2003) and a higher rate of smooth pursuit eye movement abnormalities in relatives (Sporn *et al.*, 2005). Most importantly for the present study is that COS is associated with lower cognitive levels and more prominent and widespread social and early

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developmental delays and abnormalities (Alaghband-Rad *et al*., 1995), presumably reflecting a greater degree of impairment in early brain development in COS than for more typical adult-onset patients. Attempts to identify the genes responsible for the etiology of schizophrenia and related psychoses, through linkage and candidate gene studies, have been the focus of much effort. To date, several genome-wide linkage scans and numerous candidate gene studies for schizophrenia have been published (Lewis *et al*., 2003). None of these studies has revealed a single-gene of major effect for schizophrenia, but there is growing support for the influence of a number of specific susceptibility genes (Williams *et al*., 2004).

The gene dysbindin (DTNBP1), on 6p22.3, was identified through a systematic linkage disequilibrium mapping effort by Straub *et al*. (2002). Several studies implicate significant associations between schizophrenia and certain haplotypes of single-nucleotide polymorphisms (SNPs) in the gene encoding dysbindin such as the studies in Germany and Israel (Schwab *et al*., 2003), China (Tang *et al*., 2003), Bulgaria (Kirov *et al*., 2004), and in a large case–control study of Caucasian subjects born in Ireland and the UK (Williams *et al*., 2004).

The current study evaluated single nucleotide polymorphisms (SNPs) in and around the *DTNBP1* locus in the NIMH sample of children and adolescents with schizophrenia and psychosis NOS, and their available parents. The relationships between SNP alleles and clinical phenotypes, and cognitive and premorbid endophenotypes were examined.

METHODS

Subjects

The NIMH Institutional Review Board approved the project and written consent was obtained from parents and assent from minor subjects. Patients meeting the American Psychiatric Association DSM-III-R/DSM-IV criteria for schizophrenia or psychosis NOS were recruited nationwide through an extensive screening process, including a review of over 1400 charts and in-person screening of over 230 subjects. Seventy-two of the patients who participated were diagnosed with schizophrenia with premorbid full-scale IQ of 70 or above and an onset of psychosis before their 13th birthday. The diagnosis of childhood-onset schizophrenia (COS) was confirmed by an extensive evaluation that included clinical and structured interviews of the children and parents using portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-E and K-SADS-PL) and in-hospital observation during a 1–3 week medication-free period.

In addition to clinical diagnosis, information on these subjects included cognitive and behavioral ratings of early development, history of medication response, neuropsychological test performance, and smooth pursuit eye movements. The remaining 30 children and adolescents were diagnosed as psychosis—not otherwise specified (NOS) and have been termed as multidimensionally impaired (MDI) (Kumra *et al*., 1996). These patients all had onset of psychotic symptoms by age 12, but did not meet full criteria for schizophrenia (American Psychiatric Association DSM-III-R/DSM-IV). Upon follow-up, about half of these patients have developed bipolar disorder, and none has converted to schizophrenia (unpublished data). Details of the sample characteristics are given elsewhere (Addington *et al*., 2004; Sporn *et al*., 2004), but briefly, approximately two-thirds of the sample is male, and 58% is Caucasian.

Age of onset of first psychotic symptoms was obtained through interview and patient records. Cognitive testing was completed using the Wechsler Intelligence Scale for Children – Revised (WISC-R) or Wechsler Intelligence Scale for Children – Third Edition (WISC-III). Premorbid development (defined as development from birth up to 1 year before onset of psychosis) was evaluated based on clinical, neuropsychological, and school records, standardized rating scales and parental recall. These were of particular interest as early onset cases show particularly striking early cognitive and social developmental impairment (Nicolson & Rapoport, 1999). Ratings for early language, social, and educational adjustment were also completed using a modification of the ratings by Hollis (Hollis, 1995a). The Premorbid Adjustment Scale (PAS) (Cannon-Spoor, Potkin, & Wyatt, 1982) and the Autism Screening Questionnaire (ASQ) (Berument, Rutter, Lord, Pickles, & Bailey, 1999) which have good discriminative validity with respect to the separation of Pervasive Developmental Disorder (PDD) from non-PDD diagnoses at all IQ levels, were completed through parental interviews and chart review.

Clinical/Developmental Measures for COS

The Premorbid Adjustment Scale (PAS) is designed to evaluate the degree of achievement of

developmental goals at each of several periods of a person's life before the onset of schizophrenia. Due to the severe impairment in psychological functioning of schizophrenics, considerable research has been focused on patient's psychosocial functioning preceding the onset of the schizophrenic illness, known as the prodromal period. The prodromal period is highly variable, lasting from a few months to years, though it is generally considered to be 1 year prior to the onset of the first psychotic symptoms (Beiser, Erickson, Fleming, & Iacono, 1993; Cornblatt, Lencz, & Obuchowski, 2002; Loebel *et al*., 1992). Premorbid development covers the earlier period from birth to onset of symptoms. Because COS typically has an insidious onset and "episodes" are lacking, it is often difficult to distinguish prodrome from the long, often abnormal, period of premorbid development. The PAS is especially important for the study of COS since COS is characterized by greater early developmental impairment (Alaghband-Rad *et al*., 1995). The PAS was used during screenings at the NIMH to evaluate the level of functioning in the areas of: sociability and withdrawal, peer relationships, interests, scholastic performance, and adaptation to school (Cannon-Spoor *et al*., 1982). These areas are evaluated relative to age-appropriate functioning, as is essential for pediatric samples. Each component is scored on a scale from 0 (good)–6 (poor) and a total score was computed by summing the five sections.

Nucleic Acid Purification and PCR

DNA was available for 102 children and adolescents who participated in the COS study. Seventy-three patients (72%) had both parents and 19 patients (19%) had one parent available to participate. Therefore, 92 families were included in the analyses presented in this report. Genomic DNA was extracted from immortalized lymphoblastoid cells using the QIAamp DNA Extraction Kit (Qiagen, Inc., Valencia, CA). SNPs in and around the *DTNBP1* locus (see Table I) were selected from the previous report of Straub *et al*. (2002), the dbSNP and Celera databases, and from our own re-sequencing project (unpublished data). Primer Express Software (Applied Biosystems) was used to design *Taq*Man (fluorogenic 5′ nuclease assay) primers and probes. Reactions were performed in a 384-well format in a total reaction volume of 10 μL with 2.0 ng of dried genomic DNA, 0.5 μL of 2× Ampli*Taq* Gold PCR Master Mix (Applied Biosystems), 0.1 μL of each (1000 nM) primer, 0.02 μL of each (100 nM) probe and 3.76 μL of 1× TE Buffer. The plates were then placed in a thermal cycler (PE 9700; Applied Biosystems) and were heated at 50°C for 2 minutes, then heated at 95°C for 10 minutes, followed by 40 cycles of 95°C for 30 seconds and 60°C for 1 minute. Then the plates were transferred to the Prism 7900HT, in which the fluorescence intensity in each well of the plate was read.

Statistical Analysis

Error checking was carried out with the program MERLIN (Abecasis, Cherny, Cookson, & Cardon, 2002). We measured linkage disequilibrium (LD) between markers with the D' and r^2 statistics from all Caucasian parental haplotypes by use of the program ldmax within the GOLD software package. None of the SNPs deviated from Hardy–Weinberg equilibrium. Phase known TDT, where counts of allele transmissions from heterozygous parents at each SNP locus and 2-SNP haplotypes, using ETDT, were analyzed with the TDTPHASE program version 2.37 (Dudbridge, 2003). We also used the E-M algorithm in TDTPHASE for unknown phase haplotype estimation. We tested two-marker haplotypes for association in a sliding window across the locus. All p values were computed empirically with 10,000 permutations. We carried out tests of association to quantitative traits using the QTDT program, which allowed variance-components testing of family-based samples for association and transmission disequilibrium (Abecasis, Cardon, & Cookson, 2000; Cardon, 2000). The orthogonal model used is robust to population stratification. In order to protect against possible inaccuracies due to deviations from either normality or selection on the trait, empirical p values derived from 10,000 permutations are reported.

RESULTS

Diagnosis and Childhood-Onset Psychosis

We tested a total of 14 SNPs in the gene, including 3 SNPs that showed the most positive associations in previous studies (Straub *et al*., 2002; Schwab *et al*., 2003). The marker locations and characteristics are shown in Table I.

Only one SNP, P3521, which is located in the 5′ UTR region of the gene, showed an association with the clinical phenotype, with the common allele, A, on

Table I. SNP Information

Straub 2002	NIMH P#	Inter-marker distances	Distance from P3230	SNP ID	Coding SNP	Minor allele freq	SNP-description	Chr 6. position April 2003 UCSC Freeze	COS *p*-value	Straub *p*-value**	Schwab *p*-value***
	P3230	0	0	rs1047631	A/G	.18	3′ UTR	15585640	n.s.		
P1328	P2387	1379	1379	rs742106	C/T	.29	Intron 9	15587019	n.s.	n.s.	n.s.
	P3236	61652	63031	rs12524251	T/C	.11	Intron 7	15648671	n.s.		
P1655	P2018	34723	97754	rs2619539	C/G	.44	Intron 5	15683394	n.s.	.0008	n.s.
	P2381	6698	104452	rs16876738	G/C	.13	Intron 5	15690092	n.s.		
P1635	P2163	549	105001	rs3213207	A/G	.13	Intron 4	15690641	n.s.	.00004	n.s.
P1325	P2211	5330	110331	rs1011313	G/A	.09	Intron 4	15695971	n.s.	.01	n.s.
	P3762	190	110521	rs6924627	G/A	.26	Intron 4	15696161	n.s.		
P1320	P2215	17510	128031	rs760761	C/T	.31	Intron 3	15713671	n.s.	.0004	.0007
P1763	P1763	2517	130548	rs2619522	T/G	.28	Intron 1	15716188	n.s.	n.s.	n.s.
	P3521	9469	140017	hCV3114520	A/G	.22	5′ UTR	15725657	.014 (26/11)*		
	P3587	1295	141312	hCV3114519	T/C	.19	5′ Flanking region	15726952	n.s.		
	P4211	796	142108	rs2619538	A/T	.43	5′ Flanking region	15727748	n.s.		
	P3593	4089	146197	rs742206	A/G	.15	5′ Flanking region	15731837	n.s.		

SNP – Single nucleotide polymorphism.
UCSC – University of California Santa Cruz, Genome Bioinformatics, http://genome.ucsc.edu/
*P3521 common allele overtransmitted to affecteds (26 transmited, 11 not transmitted).
**Rare alleles overtransmitted to affecteds.
***Common allele of P1320 overtransmitted to affecteds.

the coding strand being over-transmitted to affecteds (Transmitted = 26, Not transmitted = 11; $p = .014$). The two 2-marker haplotypes containing P3521 also showed association, though in each case it was the undertransmitted haplotypes containing the rare allele of marker P3521 that showed the greatest significance ($p = .021$, .008). No other haplotypes tested showed association. The strength of the marker-to-marker LD at this locus is highly variable as shown in Table II.

Analysis of Endophenotypes

In addition to the association with clinical phenotype, the common allele of SNP P3521 was associated with an older age of onset of psychotic symptoms ($p = .01$). Table III shows that there were several other significant associations resulting from the QTDT analyses. The common allele of P3521 was associated also with poorer social withdrawal and impaired peer relationships scores on the PAS. Further, the rare alleles of the three SNPs immediately upstream of P3521, namely P3762, P2215, and P1763, all showed significant associations with poorer scores on each of the subcomponents, as well as total scores, on the PAS ($p = .0009$–.002).

DISCUSSION

Endophenotypes have proven to be useful constructs in the genetic analysis of adult psychiatric disorders and cognition (for example evaluation of the working memory Catechol-O-methyltransferase (COMT) gene (Weinberger, 1999; Weinberger *et al.*, 2001), and thus may be a cognitive endophenotype for schizophrenia). Children who are known to be at risk for, or already have a disorder similar to the adult psychiatric disorder, may turn out to be a particularly attractive population to evaluate the role of endophenotypes in genetic studies (Skuse, 2001). Studies have shown that children being treated for psychiatric disorders who subsequently develop schizophrenia were more likely to be socially withdrawn and isolated than children with other disorders (Cannon *et al.*, 2001). Our nonspecific measures of early development and cognition likely reflect differences in brain development. Since schizophrenia is widely considered a developmental disorder (Weinberger, 1987), risk genes for schizophrenia are expected to act, at least in part, through disruption of normal neurodevelopmental processes and indeed this may be what we have observed in the present study.

Table II. Positive ($p < .1$) QTDT Associations by SNP and Phenotype

Marker	Risk allele	Sociability and withdrawal	Peer relationships	Interests	Scholastic performance	Adaptation to school	PAS-total
P3230		n.s.	n.s.	n.s.	n.s.	n.s.	.020
P2387	1	n.s.	.052	.045	n.s.	.028	n.s.
P3236	2	n.s.	.015	n.s.	n.s.	n.s.	n.s.
P2018		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
P2381		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
P2163	2	.032	n.s.	n.s.	n.s.	n.s.	n.s.
P2211	2	.033	n.s.	n.s.	n.s.	n.s.	n.s.
P3762	2	.036	.001	.029	.046	.028	.001
P2215	2	.012	.004	.005	n.s.	.028	.001
P1763	2	.045	.005	.025	n.s.	.029	.003
P3521	1	.006	.013	n.s.	n.s.	n.s.	.045
P3587		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
P4211		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
P3593		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

n.s. – Not significant.
Note: The rare allele was associated with higher scores, indicating poorer functioning, on all scales for all SNPs, with the exception of P2387 and P3521.

Table III. D' Values and (r^2) for All Combinations of the 14 SNPs Spanning the DTNBP1 Locus Included in this Study

	P3230	P2387	P3236	P2018	P2381	P2163	P2211	P3762	P2215	P1763	P3521	P3587	P4211	P3593
P3230														
P2387	.025 (.000)													
P3236	1.000 (.021)	1.000 (.038)												
P2018	.891 (.186)	.540 (.118)	1.000 (.097)											
P2381	1.000 (.029)	1.000 (.055)	1.000 (.815)	1.000 (.127)										
P2163	.892 (.721)	.046 (.000)	1.000 (.020)	1.000 (.214)	.999 (.026)									
P2211	.250 (.001)	.268 (.003)	1.000 (.010)	1.000 (.092)	1.000 (.014)	.999 (.017)								
P3762	.820 (.44)	.085 (.001)	1.000 (.033)	.299 (.033)	1.000 (.045)	.928 (.546)	1.000 (.029)							
P2215	.843 (.458)	.152 (.003)	1.000 (.033)	.241 (.021)	1.000 (.042)	1.000 (.595)	1.000 (.032)	1.000 (.963)						
P1763	.841 (.442)	.127 (.002)	1.000 (.033)	.197 (.015)	1.000 (.042)	1.000 (.575)	1.000 (.032)	1.000 (.963)	1.000 (1.000)					
P3521	.392 (.012)	.487 (.035)	.037 (.000)	.797 (.216)	.174 (.011)	.338 (.007)	.996 (.034)	.796 (.080)	.739 (.067)	.748 (.068)				
P3587	1.000 (.033)	.037 (.001)	1.000 (.014)	.839 (.099)	1.000 (.019)	1.000 (.028)	.397 (.002)	.595 (.187)	.528 (.124)	.504 (.122)	1.000 (.069)			
P4211	.705 (.073)	.199 (.022)	.583 (.045)	.277 (.056)	.185 (.007)	.600 (.048)	1.000 (.141)	.676 (.097)	.690 (.111)	.697 (.113)	.924 (.216)	.790 (.072)		
P3593	1.000 (.027)	.019 (.000)	1.000 (.012)	.807 (.074)	1.000 (.016)	1.000 (.024)	.584 (.004)	.686 (.209)	.629 (.145)	.629 (.145)	1.000 (.051)	1.000 (.852)	.748 (.052)	

Shaded blocks indicate $p < .01$.

Adult patients with schizophrenia have been shown to demonstrate subtle but significant impairments in premorbid development (Done, Crow, Johnstone, & Sacker, 1994; Jones, Rodgers, Murray, & Marmot, 1994), and since childhood-onset schizophrenia appears to represent a more malignant form

of the disorder, with more pronounced premorbid abnormalities (language delays, learning disorders, and disruptive behavior) than are observed in adult-onset patients (Alaghband-Rad *et al*., 1995; Hollis, 1995b; Nicolson & Rapoport, 1999; Nicolson *et al*., 2003;), the present pattern of associations would suggest these findings may be genetically mediated.

In the current study, SNP P3521, which is in the 5′ untranslated region (UTR) of dysbindin, was associated with the clinical diagnosis of childhood onset psychosis. The location of this SNP in the mRNA makes it a candidate as a functional variant for effective expression. Alternatively, P3521 could be in linkage disequilibrium with a variant elsewhere in the gene. The current study also builds on considerable evidence for the continuity between childhood and adult onset schizophrenia (see Nicolson & Rapoport, 1999). Now the clinical continuity is extending to genetic associations as we have recently replicated associations with two other schizophrenia susceptibility genes, G72 (13q34) (Addington *et al*., 2004) and GAD1 (2q31) (Addington *et al*., 2005).

Six SNPs from the previous study done by Straub *et al*. (2003) were tested in the current study. In the Straub study, the association with clinical diagnosis increased for three of the six SNPs as diagnosis categories expanded from *narrow* (D1–D2) to *very broad* (D1–D9). These findings support the idea that variations in DTNBP1 may affect individuals with modest neurodevelopmental impairment not just narrowly defined schizophrenia. Straub *et al*. found that the rare alleles were overtransmitted to affecteds. This data is in contrast to the study by Schwab *et al*. (2003) where the common allele of P1320 was overtransmitted to affecteds, indicating that there may be more than one disease mutation that may lie on a different haplotype. Since then, several positive studies in various European and Chinese populations, using both case–control and family study designs have been reported on DTNBP1 (Tang *et al*., 2003; Van Den Bogaert *et al*., 2003; Kirov *et al*., 2004, Williams *et al*., 2004). All of these studies observed the most significant associations with the common alleles and haplotypes, which implicates a complex haplotype pattern in the Dysbindin gene.

A recent study by Li *et al*. (2003) found that a deletion of DTNBP1 causes the metabolic disease Hermansky–Pudlak syndrome. While patients with Hermansky–Pudlak syndrome have no overt psychiatric symptoms indicative of schizophrenia, this does not contradict the evidence that DTNBP1 is a susceptibility gene for schizophrenia. The pattern of inheritance of schizophrenia indicates that it is not a monogenic disorder, but rather results from the interaction of many genes and environmental factors, which suggests that any single gene alone will provide merely one piece in the pathogenic puzzle. In other words, for any given disease mutation, the penetrance is likely low and the allele itself will not be sufficient to cause disease.

The observation that SNPs in DTNBP1 were associated with premorbid functioning is of particular interest, as the social, motor, and cognitive delays in the premorbid development of schizophrenia are assumed to reflect impaired early brain development. The more severe premorbid functioning in cases of childhood-onset schizophrenia may indicate a more severe early disruption of brain development, and perhaps that the susceptibility genes are more fully penetrant than in adult onset cases. Four of the 14 SNPs tested showed association with the endophenotypes, compared to only one associated with the clinical phenotype. This suggests, in general, that the relationship between genetic variations and endophenotypes that accompany schizophrenia may be easier to detect than their relationship to the clinical phenotype itself. It is anticipated that such an enhanced "signal to noise ratio" will prove valuable in the identification and characterization of schizophrenia susceptibility genes in the future. When the important genetic variations in dysbindin are fully characterized, it will be interesting to see just how different the spectrum of dysbindin susceptibility haplotypes is between adult-onset and childhood-onset patients, and how they relate to the underlying pathophysiology.

As in most studies of rare diseases, many limitations exist. The children selected for this study were nationally recruited for an inpatient treatment trial. This group consisted of severely ill, treatment refractory subjects, and thus may not be representative of early-onset subjects in general. The sample also included children with the broader phenotype, i.e., children who have psychosis but who are not necessarily schizophrenic. It is also hard to determine to what degree these SNPs influence disease without verifying whether or not the polymorphisms are functional mutations. We did not look for functional mutations mainly because this would need to be done through expression studies and protein analysis and will need to be explored in future studies. The small size of the sample greatly limits the power to detect associations, thus many of the SNPs that did not

demonstrate association with either the clinical or endophenotypes may eventually do so in larger samples, and such efforts are now underway by at least two other research groups.

There are many other unresolved issues in the study of the genetics of COS, and schizophrenia more generally, that need to be further investigated. The realization that many of the genetic disorders that were described previously as monogenic are in fact the product of defects at a small number of loci creates conceptual and practical problems like reorganization of approaches to studying complex genetic disorders. Another major unresolved issue in genetics is the impact of gene/environment interactions. In particular, whether or not age of onset is independent of the disease remains to be elucidated. A study of complex traits in twins suggested the presence of both additive genetic and common environmental effects in the etiology of schizophrenia (Kendler *et al*., 2003). In closing, we note that one of the broader implications from this work is that schizophrenia risk genes should be examined in patient populations with a range of developmental disabilities, considerably wider than just those of schizophrenia and the schizophrenia spectrum.

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