Polymorphisms in the 13q33.2 Gene *G72/G30* Are Associated with Childhood-Onset Schizophrenia and Psychosis Not Otherwise Specified

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Background: *Childhood-onset schizophrenia (COS), defined as onset of psychotic symptoms by age 12 years, is a rare and severe form of the disorder that seems to be clinically and neurobiologically continuous with the adult disorder.*

Methods: *We studied a rare cohort consisting of 98 probands; 71 of these probands received a DSM-defined diagnosis of schizophrenia, and the remaining 27 were diagnosed as psychosis not otherwise specified (NOS) (upon 2–6 year follow-up, 13 have subsequently developed bipolar disorder). Two overlapping genes,* G72 *and* G30 *on 13q33.2, were identified through linkage-disequilibrium-based positional cloning. Single nucleotide polymorphisms (SNPs) at the* G72/G30 *locus were independently associated with both bipolar illness and schizophrenia. We analyzed SNPs at this locus with a family-based transmission disequilibrium test (TDT) and haplotype analyses for the discrete trait, as well as quantitative TDT for intermediate phenotypes, using the 88 probands (including COS and psychosis-NOS) with parental participation.*

Results: *We observed significant pairwise and haplotype associations between SNPs at the* G72/G30 *locus and psychotic illness. Furthermore, these markers showed associations with scores on a premorbid phenotype measured by the Autism Screening Questionnaire, and with age of onset.*

Conclusions: *These findings, although limited by potential referral bias, confirm and strengthen previous reports that* G72/G30 *is a susceptibility locus both for schizophrenia and bipolar disorder.*

Key Words: Candidate gene, genetic association, transmission disequilibrium test, quantitative transmission disequilibrium test, schizophrenia, children

Childhood-onset schizophrenia (COS), defined as onset of psychotic symptoms by age 12, is a rare and severe form of the disorder (Nicolson and Rapoport 1999). The prevalence of COS is estimated to be 1/300 of the adult rate (McKenna et al 1994). Since 1990, patients with COS have been recruited nationally at the National Institute of Mental Health (NIMH) for clinical and neurobiological studies. Childhood-onset schizophrenia seems to be clinically and neurobiologically continuous with the adult disorder (Nicolson and Rapoport 1999). Stratification by age of onset might serve to identify a more homogeneous patient group, less confounded by the secondary effects of illness, such as institutionalization and substance abuse, and with a more salient genetic risk (Childs and Scriver 1986). Compared with adult-onset patients, the COS population more clearly shows a higher rate of familial spectrum disorder (Asarnow et al 2001; Nicolson et al 2003), a higher rate of smooth pursuit eye movement abnormalities in relatives (unpublished data), and in general, lower cognitive levels. Childhood-onset schizophrenia is also associated with more prominent early developmental abnormalities (Alaghband-Rad et al 1995), such as language and motor impairment, resembling pervasive developmental disorders (PDD), but presumably this reflects more impaired early brain development. Thus, COS seems to be quantitatively, but not qualitatively, different from the more typical adult-onset disorder (Sporn et al, in press).

There is growing support for the influence of specific susceptibility genes for schizophrenia (Harrison and Owen 2003). Converging linkage evidence from multiple independent studies suggested that region 13q32-33 contains susceptibility gene(s) for both schizophrenia and bipolar disorder (Badner and Gershon 2002). Chumakov et al (2002) used a case–control linkage disequilibrium-based positional cloning approach to identify overlapping genes *G72* and *G30* in this region. Reverse transcriptase polymerase chain reaction (PCR) indicated that both *G72* and *G30* generate numerous splice variants in various parts of brain, spinal cord, and testis. By yeast two-hybrid experiments with the *G72* protein, Chumakov et al (2002) identified the enzyme D-amino acid oxidase (DAO) as an interacting partner. D-amino acid oxidase is expressed in human brain, where it oxidizes D-serine, a potent activator of *N*-methyl-D-aspartate-type glutamate receptors. The *G72* gene has subsequently been named D-amino acid oxidase activator. Polymorphisms in and near these genes were reported to be associated with schizophrenia in both French Canadian ($p = 3 \times 10^{-6}$) and Russian ($p = .0004$) patient samples. Recently, Hattori et al (2003) reported association between haplotypes in the *G72/G30* locus and bipolar disorder in two independent samples of multiplex bipolar disorder families ($p = .0004$ and $p = .008$). The notion that schizophrenia and bipolar disorder, and perhaps psychosis more generally, might share some underlying susceptibility genes has been a common theme in recent psychiatric genetics literature (Berrettini 2000).

This study evaluated SNPs in and around the *G72/G30* locus in the NIMH sample of children and adolescents with schizophrenia and psychosis–not otherwise specified (NOS) and their available parents. Our hypothesis was that there would be overtransmission of alleles to affected individuals, consistent

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Table 1. Sample Characteristics

	Childhood-Onset Schizophrenia	Childhood-Onset Psychosis NOS (MDI)	Combined Sample
Total *N*	71	27	98
Caucasian	35	22	57
Non-Caucasian	36	5	41
Full Trios	53	16	69
Dyads	11	8	19
Singletons	7	3	10
N used for TDT	64	24	88

NOS, not otherwise specified; MDI, multidimensionally impaired; TDT, transmission disequilibrium test.

with those markers and alleles reported in the adult patient samples.

Methods and Materials

Patient Recruitment and Clinical Assessment

Deoxyribonucleic acid (DNA) was available for 98 children and adolescents who participated in the COS study (Nicolson and Rapoport 1999). Ninety percent of the patients had at least one parent available to participate as well (Table 1).

Given the rarity of these patients, the ethnic background was quite mixed: approximately half the sample was Caucasian, another quarter were African American, and the remaining were a mix of Hispanic, Asian, and Indian. The project was approved by the NIMH Institutional Review Board; written consent was obtained from parents and assent from minor subjects. Patients meeting DSM-III-R/DSM-IV (American Psychiatric Association 1994) criteria for schizophrenia or psychosis-NOS were recruited nationwide through an extensive screening process, including a review of more than 1400 charts and in-person screening of more than 230 subjects. All patients included in the study were required to have a premorbid full-scale intelligence quotient (IQ) of 70 or greater and an onset of psychosis by age 12 years. Seventy-one of the patients who participated were diagnosed with schizophrenia. The diagnosis of COS was confirmed by two psychiatrists ($\kappa = .8$) (McKenna et al 1994) through an extensive evaluation that included clinical and structured interviews of the children and parents with portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Present and Lifetime Version and Epidemiologic Version) (Ambrosini 2000; Kaufman et al 1997) and in-hospital observation during a 1–3-week medication-free period. 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 27 children and adolescents were diagnosed as psychosis-NOS and have been termed multidimensionally impaired (MDI) (Kumra et al 1998). These patients all had onset of psychotic symptoms by age 12 but did not meet full criteria for schizophrenia (McKenna et al 1994). Upon 2–6-year follow-up, 13 of these 27 patients have subsequently developed bipolar disorder (unpublished observations).

Age of onset of first psychotic symptoms was obtained through interview and patient records. Cognitive testing was completed with the Wechsler Intelligence Scale for Children–Revised or Wechsler Intelligence Scale for Children–Third Edition. Premorbid development (defined as development up to 1 year before onset of psychosis) was evaluated on the basis of clinical, neuropsychological, standardized rating scales, school records, and parental recall. This information was of particular interest because early-onset cases show more striking early developmental impairment (Nicolson and Rapoport 1999). Ratings for early language, social, and educational adjustment were also completed with a modification of the ratings by Hollis (1995). In addition, the Premorbid Adjustment Scale (Cannon-Spoor et al 1982) and the Autism Screening Questionnaire (ASQ), which has good discriminative validity with respect to the separation of PDD from non-PDD diagnoses at all IQ levels (Berument et al 1999), were completed through parental interviews and chart review.

Nucleic Acid Purification and PCR

Genomic DNA was extracted from immortalized lymphoblastoid cells with the QIAamp DNA Extraction Kit (Qiagen, Valencia, California). Single nucleotide polymorphisms in and around the *G72/G30* locus were selected from the reports of Chumakov et al (2002) and Hattori et al (2003) and are detailed in Table 2. In addition, three SNPs in the *DAO* locus were tested: MDAAO-4, MDAAO-5, and MDAAO-6, from Chumakov et al (2002). We used Primer Express Software (Applied Biosystems, Foster City, California) 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 reaction with 2.0 ng of dried genomic DNA, 5 μL of 2× Ampli*Taq* Gold PCR Master Mix

Table 2. TDT by Locus

SNP	ID	Coding Strand SNP[a]	Major Alelle Frequency[b]	Physical Location[c]	InterSNP Distance (bp)	COS Only (T/NT)[d]	MDI Only (T/NT)	Combined (T/NT)	Transmission Ratio	Two-Sided *p*	Chumakov *p*	Hattori *p*
1	rs746187 (M-7)	A/G	.62	104,835,310	0	27/21	5/1	32/22	1.45	.172	ns	nd
2	rs3916964 (M-11)	G/A	.54	104,916,071	80761	27/22	5/6	32/28	1.14	.605	.062	nd
3	rs1935058	C/T	.55	104,947,988	31917	32/17	6/6	38/23	1.65	.054	nd	<.001
4	rs3916967 (M-14)	T/C	.60	104,953,986	5998	30/16	7/3	37/19	1.95	.015	.038	nd
5	rs2391191 (M-15)	C/T	.61	104,956,084	2098	29/17	7/3	36/20	1.80	.031	.032	.080
6	rs1935062	A/C	.65	104,964,774	8690	27/18	7/6	34/24	1.42	.188	nd	.008
7	rs778294 (M-19)	C/T	.77	104,978,873	14099	17/24	4/6	21/30	.70	.206	ns	.018
8	rs778293 (M-22)	T/C	.52	105,005,837	26964	31/25	6/6	37/31	1.19	.467	.003	nd

TDT, transmission disequilibrium test; SNP, single nucleotide polymorphism; ID, identifier; bp, base pair; COS, childhood-onset schizophrenia; MDI, multidemensionally impaired; T, transmitted; NT, not transmitted; ns, not significant; nd, not done.

[a]Major allele listed first.

[b]Calculated from the nontransmitted parental chromosomes in the total data set.

[c]UCSC Browser, April 2003; http://genome.ucsc.edu/cgi-bin/hgGateway.

[d]Counts of transmitted and nontransmitted alleles from heterozygous parents to affected offspring.

Table 3. Two-SNP Haplotype Results

		Phase-Known TDTPHASE				Phase-Unknown TDTPHASE			Phase-Unknown TRANSMIT		
	Haplotype	T/NT	Haplotype *p*	Global *p*	Transmission Ratio	T/NT	Haplotype *p*	Global *p*	Obs/Exp	Haplotype *p*	Global *p*
SNP 1-2				.595				.633			.477
SNP 2-3	C-C	18/11	.234	.561	1.636	60/46	.102	.072	60/53	.065	.072
SNP 3-4	C-A	28/11	.015	.051	2.545	106/80	.009	.029	104/92	.009	.013
SNP 4-5	A-G	28/11	.013	.013	2.545	129/107	.020	.030	124/114	.008	.004
SNP 5-6	G-A	25/11	.032	.055	2.273	116/101	.090	.072	116/108	.066	.059
SNP 6-7	A-A	21/11	.118	.163	1.909	51/40	.196	.384	51/45	.107	.189
SNP 7-8				.259				.637			.597

T, transmitted; NT, not transmitted; Obs, observed; Exp, expected; SNP, single nucleotide polymorphism.

(Applied Biosystems), .1 μL of each primer, .02 μL of each 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 min, then heated at 95°C for 10 min, followed by 40 cycles of 95°C for 30 sec and 60°C for 1 min. Then the plates were transferred to the Prism 7900HT (Applied Biosystems), in which the fluorescence intensity in each well of the plate was read.

Statistical Analysis

We carried out error checking with the program MERLIN (Abecasis et al 2002; http://www.sph.umich.edu/csg/abecasis/Merlin/). We measured linkage disequilibrium (LD) between markers with the D′ and Δ^2 statistics from parental haplotypes by use of the program ldmax within the GOLD software package (Abecasis and Cookson 2000). None of the SNPs deviated from Hardy-Weinberg equilibrium. Phase-known transmission disequilibrium test (TDT), which are carried out with data on transmissions from heterozygous parents to affected offspring, were completed with the TDTPhase program, version 2.37 (Dudbridge 2003; http://www.hgmp.mrc.ac.uk/Registered/Option/unphased.html). To determine whether more power could be gained by use of the E-M algorithm for unknown phase haplotype estimation, we used two programs: TDTPhase and TRANSMIT (Clayton 1999; http://www-gene.cimr.cam.ac.uk/clayton/software/), version 2.5.4, and compared the results from the different algorithms. We tested two-marker haplotypes for association in a sliding window across the locus. All *p* values were computed empirically within each program with 10,000 permutations or bootstrap replicates, respectively. We carried out tests of association to quantitative traits using the QTDT program (http://www.sph.umich.edu/csg/abecasis/QTDT/index.html), which allowed variance-components testing of family-based samples for association and transmission disequilibrium (Abecasis et al 2000). The orthogonal model used is robust to population stratification. 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

Results from the pairwise TDT analyses are detailed in Table 2.

Given the a priori hypothesis that the *G72* gene might play a role in the development of both schizophrenia and bipolar disorder, and the observation that most of the SNPs showed a similar pattern of transmission in each of the COS and MDI groups, the samples were combined for all remaining analyses, though analyses using the COS group alone provided similar results (available upon request). As shown in Table 2, SNPs 3, 4, and 5 showed significant LD with illness ($p = .05$, .015, and .03, respectively). In each case, the common allele confers risk, consistent with previous reports (Chumakov et al 2002; Hattori et al 2003). The most significant SNP, rs3916967, had a transmission ratio of approximately 2. None of the *DAO* markers showed any significant associations ($p = .62$–.87; results not shown).

Strong LD was observed between the SNPs 3–7, consistent with the reports of Chumakov et al (2002) and Hattori et al (2003) (see Appendix 1). Given the knowledge that LD between closely spaced markers tends to be less strong in African populations, we also computed LD using the African American families only and did in fact find less LD. In this subsample, strong LD extended only between SNPs 4–6. We tested the transmission of two SNP haplotypes in relation to illness (Table 3).

The haplotype analyses did not show greater significance over the pairwise analyses, though in the phase-known analyses, the transmission ratios, which can be interpreted as the relative risk, of the common haplotypes for the SNP3-4 and SNP4-5 combinations were higher, at 2.5, than the single-marker risk of 1.95. The neighboring haplotypes also showed trends toward significance (see Table 3). We tested two different algorithms for estimation of unknown phase haplotypes, which essentially produced the same results, although the *p* values from TDTPhase were slightly larger than those from TRANSMIT.

Table 4. QTDT Results

	Age of Onset of Psychotic Symptoms	Autism Screening Questionnaire
N	88	73
Average	9.31	7.56
SD	2.29	8.32
SNP 1	ns	.028
SNP 2	ns	ns
SNP 3	.017[a]	.038[b]
SNP 4	.020[a]	.010[b]
SNP 5	.030[a]	.011[b]
SNP 6	.002[a]	.004[b]
SNP 7	ns	ns
SNP 8	ns	ns

QTDT, quantitative transmission disequilibrium test; SNP, single nucleotide polymorphism.

[a]Diagnostic risk allele associated with older age of onset.

[b]Diagnostic risk allele associated with lower/better score on Autism Screening Questionnaire.

We had age of onset information on all probands but did not have complete ASQ information on all subjects; the number of families included in each of these analyses is detailed in Table 4. The quantitative TDT findings were of interest, in that significant associations were seen with several SNPs, which were in LD with each other, and both age of onset of psychosis ($p = .002–.017$) and ASQ score ($p = .003–.02$) (Table 4).

In every case, the risk allele found to be associated with the clinical phenotype was associated with later age of onset and lower ASQ score, indicating an age of onset closer to adolescence with fewer premorbid developmental disturbances. This suggests that the patients in this sample who inherit the "risk" allele might in fact more closely resemble the more common adolescent/adult-onset cases of schizophrenia rather than the more extreme developmentally impaired group.

Discussion

We report a positive association between the *G72/G30* locus and childhood onset psychosis, which supports two previous reports implicating *G72/G30* as a susceptibility gene for both schizophrenia and bipolar disorder. This finding also supports the notion of continuity between this very-early-onset population and the far more common adult-onset disorder. In addition, this is the first report of an association between *G72/G30* and age of onset of psychotic symptoms and premorbid development.

We performed a power analysis using the TDT Power Calculator (Chen and Deng 2001). TDT Power Calculator (Chen and Deng 2001; http://www.biostat.jhsph.edu/~wmchen/pc.html) was used for the simulations. For the simulations, a disease gene with allele frequency of .25, and an SNP marker with allele frequency .5, in complete LD with the disease locus, and genotypic penetrances as follows: AA = .6, Aa = .3, and aa = .1, were used as model parameters. The simulation revealed that that the present sample had 74% power to detect a locus for $p < .05$. Although one must always consider the possibility of type I error, given that we observed overtransmission of the same alleles in the same markers previously reported by independent groups, we think this is highly unlikely.

The *G72/G30* locus appears to be contained within one of the linkage "peaks," logarithm of odds (LOD) = 1.68, in the genome-wide linkage analysis of age of onset of schizophrenia by Cardno et al (2001). The LOD curve in the Cardno report maximized at the marker D13S158, which is 2 Mb proximal to *G72*. This analysis suggested that the 13q region might contain a putative quantitative trait locus for age of onset of schizophrenia; the analysis did not, however, discriminate between earlier or later onset, but rather for increased similarity of age of onset among affected siblings. Although it is intriguing that we found an association between SNPs and age of onset, this relationship is difficult to interpret, given that our oldest age of onset was 12, which is still well below the age of onset for more typical adolescent/adult-onset form of the disorder. Therefore, this association deserves follow-up in other samples of schizophrenic subjects. Similarly, the association with lower ASQ score we observed supports a longer period of normal development and suggests that *G72/G30* might act later than other, as yet unidentified, risk factors within this cohort.

The strategy of studying rare, early-onset cases of more common diseases has proven to be successful in identifying at least some genetic contributors to the development of other diseases, such as Alzheimer's disease and breast cancer. Intuitively, these more severe, earlier-onset cases represent a subgroup with higher genetic liability. Another advantage is that younger patients tend to have more parents available for study. One of the strengths of the current study is the rigorous phenotyping procedure, with final diagnoses only made after a 1–3-week medication-free period. Although the study of these patients might provide more power for detection of genetic effects, there are limitations to consider as well. First, given the rarity of such cases, the sample size is small, and unknown referral bias is likely (e.g., more complete families, ability to travel, less ill parents). Second, strict study designs requiring particular family structures or ethnic backgrounds were not possible. Although our sample was ethnically heterogeneous, the overall associations were maintained when we restricted the analysis to include only Caucasian families. Furthermore, when we compared the allele frequencies between Caucasian and African American probands, the risk alleles were more common in the African Americans; however, this should be confirmed in a larger sample. Another consequence of the ethnic heterogeneity is that replication of associations observed with a TDT using a case–control analysis will be difficult. Finally, although a direct comparison of the rates of transmission of risk alleles in the schizophrenic and bipolar subsamples would provide insight into the relative effects of this gene in the two disorders, this was not feasible given the limited sample we had available.

One hypothesis that might now be testable is that there is a more salient genetic effect in childhood-onset cases compared with the more typical adult-onset cases. Statistical comparison with the published studies is difficult, but examination of the results from the one marker (rs2391191) that showed at least a positive trend toward association with illness in all three studies reveals the following. The transmission ratio of 1.8 seen with this marker in the current study is slightly larger than the odds ratio of 1.34 reported by Chumakov et al (2002). And although Hattori et al (2003) did not report their actual transmission counts, we obtained these data from the authors (Eiji Hattori, personal communication) and computed an odds ratio of 1.6 for their combined Clinical Neurogenetics and NIMH samples, which again is a slightly smaller effect size than that seen in the current study. It is notable that rs2391191 is the only common SNP studied that could influence the primary structure of the LG72 protein (lys29arg). It is not appropriate, however, to argue that the overall effect size of this gene is stronger in the child sample than in the previously studied adult samples, given that the strongest association in each sample was observed at different SNPs. Finally, the finding of Chumakov et al (2002) that markers in the *DAO* locus also showed association to schizophrenia was not confirmed in the current study.

The present study supports the existence of schizophrenia/bipolar disorder–related variants at or near the *G72/G30* locus. In addition, the novel relationship we observed between SNPs at this locus and age of onset and premorbid functioning (as measured by the ASQ) deserve further exploration in adult-onset schizophrenia samples, with the use of both triad and case–control approaches.

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Appendix 1. Baackground LD in the G72/G30 Locus and Neighboring Regions

Marker	SNP 1	SNP 2	SNP 3	SNP 4	SNP 5	SNP 6	SNP 7	SNP 8
SNP 1		.02	.01	.00	.00	.01	.00	.02
SNP 2	.19		.02	.01	.02	.02	.00	.02
SNP 3	.12	.16		.54[a]	.56[a]	.34[a]	.20[a]	.01
SNP 4	.07	.14	.98[a]		.97[a]	.65[a]	.14[a]	.05
SNP 5	.06	.18	1.00[a]	.99[a]		.68[a]	.13[a]	.06
SNP 6	.08	.16	.81[a]	.85[a]	.87[a]		.13[a]	.05
SNP 7	.02	.04	.82[a]	.87[a]	.86[a]	.92[a]		.01
SNP 8	.19	.16	.11	.36	.38	.34	.19	

For each pair of markers, the standardized D′ is shown below the diagonal, and r^2 is shown above the diagonal. LD, linkage disequilibrium; SNP, single nucleotide polymorphism.

[a]Indicates region of strong LD.