ELECTRONIC LETTER

Evidence for association between single nucleotide polymorphisms in T complex protein 1 gene and schizophrenia in the Chinese Han population

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Schizophrenia (MIM 181500) is a severe, common, and heterogeneous psychiatric disorder that affects 1% of the world's population. The disorder is characterised by hallucinations, delusions, disorganised thoughts, and various cognitive and affective impairments. As a leading cause of psychiatric admissions, schizophrenia accounts for a considerable portion of healthcare expenditure and is a major public health concern.

Family, twin, and adoption studies have shown that a genetic factor is associated with susceptibility to schizophrenia.¹⁻⁴ The number and nature of genes that influence susceptibility to schizophrenic illness, as well as their interaction with environmental factors, are unknown. Despite decades of research on anatomical, physiological, and biochemical changes possibly associated with schizophrenia, insight into the aetiology is only fragmentary. Mapping of genes that contribute to the development of schizophrenic disorders by means of linkage and association studies may help identify and characterise causal factors.

Although no single causative gene has been identified to date, several chromosomal loci with positive linkage results are under investigation as tentative susceptibility loci for schizophrenia, including chromosomes 6, 8, 10, 13, and 22 to remove obstacles of locus heterogeneity among sampled populations.⁵

Cao *et al* first reported possible linkage to 6q21-22 in two independent American samples of patients with schizophrenia: at locus D6S474 using sibling pair analysis in 63 independent sibling pairs ($p = 0.00018$) and at D6S424, which is about 14 centimorgan (cM) near D6S474 in a second sample of 87 independent sibling pairs ($p = 0.00095$).⁶ The same group reported modest support for linkage to D6S424 in a third sample in 1999 that consisted of 54 American and Australian sibling pairs.⁷ In a study with combined samples (141 independent sibling pairs), they obtained a non-parametric likelihood of odds (LOD) score of 3.82 ($p = 0.000014$).⁷

Several other studies also supported a susceptibility locus for schizophrenia on chromosome 6q. The Genetics Initiative Collaborative study by the National Institute of Mental Health found evidence of linkage, although not significant, on chromosome 6q16-24; multipoint non-parametric analyses produced a $Z_{\max}$ of 1.89 ($p = 0.023$).⁸ In analyses of candidate regions on chromosomes 5q, 6q, 10p, and 13q in 734 pedigrees with 824 independent sibling pairs collected by eight research groups, Levinson *et al* found modest support for linkage to chromosome 6q21-22 (LOD score 3.10 with sibling pair analysis ($p = 0.0036$), non-parametric LOD score 2.47 ($p = 0.0046$), and recessive LOD score 2.47).⁹ In a genomewide autosomal screening of 71 families from Germany and Israel that included 86 independent affected sibling pairs with parental genotype information for statistical analysis strictly identified by descent, Schwab *et al*

Key points

- Schizophrenia is a common and heterogeneous psychiatric disorder. Many loci or candidate genes have been reported to be associated with susceptibility to schizophrenia, but so far no single causative gene has been identified successfully.
- The T complex protein 1 (*TCP1*) gene, which is highly conserved, has an important role in cytoskeletal maintenance and neurotransmitter trafficking. The higher expression of *TCP1* in the hippocampal tissue of patients with schizophrenia may indicate that it is biologically relevant to schizophrenia.
- Different statistical methods were used to examine the association between polymorphisms of *TCP1* and schizophrenia in 380 Chinese Han people with schizophrenia and 322 Chinese Han healthy controls.
- Significant differences were seen between case and control groups in the frequencies of C alleles and T alleles ($p = 0.00023$) and of CT and CC genotypes ($p = 0.011$ and $p = 0.00017$, respectively) at rs15982. An estimate of haplotype frequencies showed significant differences between cases and controls ($p = 0.000002$ on T1 test for cases and on T4 test for controls).
- *TCP1* probably plays a significant role in the pathogenesis of schizophrenia. Future studies to investigate the role of *TCP1* in schizophrenic disorders are justified. The findings support the idea of a common disease with common variant.

showed evidence of linkage on chromosome 6q with the multipoint LOD score method (LOD score 1.12 for D6S271 and LOD score 1.11 for D6S1613).¹⁰ In another study that involved an "affected only" genome scan analysis with 43 members of a pedigree with 12 generations and 3400 members, Lindholm *et al* obtained $Z_{\max}$ of 6.6 at D6S253 in the 6q25 region, as well as a 6 cM haplotype from markers D6S253 to D6S264.¹¹ A multipoint analysis was performed with the markers in the 6q25 region, and a maximum LOD score of 7.7 was obtained between markers D6S253 and D6S297.¹¹ Interestingly, a susceptibility locus for autism also has been mapped to the 6q25 region.¹² Furthermore, deletions of the 6q25 segment can result in developmental problems and anomalies of the brain.¹³ All of these results suggest that genes important for normal brain function or development, or both, and for development of schizophrenia likely are located on chromosome 6q.

Recently, numerous studies have identified disease related changes in protein expression (upregulation or downregulation).¹⁴ Genes that alter expression may underlie common and complex diseases such as hypertension, cancer, diabetes, and mental disorders. Analysis of comparative proteome in cases and controls is a new strategy to discover proteins that does not need a theory of the pathogenesis and manner of inheritance of diseases. Edgar *et al* used proteome analysis to compare the protein expression of the hippocampal proteome in seven patients with schizophrenia and seven healthy controls.^{15–16} They characterised four proteins: diazepam binding inhibitor (DBI) and manganese superoxide dismutase (Mn SOD), whose genes map to 2q12–21 and 6q25.3, respectively, and T complex protein 1 and collapsin response mediator protein 2, whose genes map to 6q25.3–26 and 8p21, respectively. Expression of DBI and Mn SOD was lower in patients with schizophrenia than healthy controls and expression of T-complex protein 1 and collapsin response mediator protein 2 was higher. Genes of the two proteins whose expression was different in the hippocampal tissue of people with schizophrenia map to 6q, which indicates that these genes may be associated with susceptibility to schizophrenia.

T complex protein 1 (*TCPI*) gene is highly conserved and ubiquitous and has an important function as a chaperonin.¹⁷ Yaffe *et al* and Ursic *et al* found that *TCPI* played a role in the folding of actin and tubulin,^{18–19} both of which are important for cytoskeletal maintenance, and had critical roles in neurotransmitter trafficking and segregation distortion.^{20–22}

To determine the association of the *TCPI* gene with schizophrenia and to find genetic bases responsible for the upregulated expression of *TCPI* in the hippocampal tissue of people with schizophrenia, we performed a case–control based association study in the Chinese Han population.

MATERIALS AND METHODS

Selection of single nucleotide polymorphisms

We chose single nucleotide polymorphisms in exon 12 and the 3' flanking region of the *TCPI* gene from the dbSNP database (<http://www.ncbi.nlm.nih.gov/SNP/>) for a number of reasons. Few single nucleotide polymorphisms were characterised in the 5' flanking region. Few single nucleotide polymorphisms are found in exons 1–11. Five single nucleotide polymorphisms are found in exon 12 (*rs4832* (A/C), *rs2957* (C/T), *rs1062660* (A/T), *rs1062659* (A/T), *rs3211255* (A/C)). Two single nucleotide polymorphisms (*rs15982* (C/T) and *rs3173126* (C/T)) are found in the 3' flanking region and have been characterised as common variants (with frequency of minor alleles >15%) in exon 12 and the 3' flanking region, respectively. Polymorphism loci in the 3' region were reported to play a regulated role in the gene expression of and be associated with the aetiology of neuropathological disorders such as Alzheimer's disease.^{23–30} For these reasons, we sequenced the whole of exon 12 and the 3' flanking region of the *TCPI* gene in our sample of sporadic cases of schizophrenia to find genetic variations that might modify the risk of schizophrenia developing.

Study participants

Patients with schizophrenia were recruited from patients with sporadic cases from psychiatric hospitals in the Shanghai and Jilin provinces; the sample included 380 patients with schizophrenia (mean age 27.2 (SD 7.9) years; 50% men). All cases fulfilled the criteria for schizophrenia in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*. Each patient was diagnosed by the consensus of at least two experienced psychiatrists. The schizophrenia unrelated healthy volunteers consisted of 322 people (mean age 30.2 (9.5) years; 49% men) who were recruited from the

same areas. All participants were Han Chinese in origin. Written informed consent was obtained from all participants, and the study was approved by the Ethnical Committee of the National Human Genome Center at Shanghai.

Genotyping of single nucleotide polymorphisms

We extracted genomic DNA from peripheral blood leucocytes by standard procedures.³¹ We used forward primer 5'-AAGCGGCCGTAAATAATTC-3' and reverse primer 5'-CTTTGGTCTCTGATTTCACA-3' (product size 404 base pairs) to assess allele and genotype frequency of five single nucleotide polymorphisms found in exon 12. We used forward primer 5'-ACTTGGGTTTTGTGATGTAGG-3' and reverse primer 5'-TTCCTCTTAATGTATCAGCATGC-3' (product size 388 base pairs) to assess the allele and genotype frequencies of two single nucleotide polymorphisms in the 3' flanking region. We carried out polymerase chain reaction (PCR) in a 25 µl reaction mixture that contained 10 ng genomic DNA, 4 pmol/l of each primer, 2.5 mmol/l magnesium chloride, 0.2 mmol/l deoxynucleoside triphosphate, and 3 units Taq polymerase (Life Technologies, Karlsruhe, Germany). An initial denaturing step of 5 minutes at 95°C was followed by 40 cycles of 94°C for 30 seconds, 54°C for 45 seconds, and 72°C for 50 seconds. A final extension step was carried out at 72°C for 10 minutes. We performed PCR cycling with a Gene Amp PCR System 9700 (Applied Biosystems, Foster City, CA, USA). We typed all seven single nucleotide polymorphisms by direct sequencing. We prepared DNA for sequencing by incubation of PCR products with 0.15 units of shrimp alkaline phosphatase (Roche, Basel, Switzerland) and 0.75 units of exonuclease I (New England Biolabs, Beverly, MA, USA) at 37°C for 60 minutes, followed by heat inactivation at 80°C for 10 minutes. We sequenced the PCR products with an ABI Prism BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) on an ABI Prism 377 and 3100 Sequencer. We confirmed all genotypes by repeat sequence assay.

Statistics

We compared allele, genotype, and haplotype frequencies with the χ^2 test. We calculated deviations from the Hardy-Weinberg equilibrium, differences in allele and genotype distributions, and odds ratios with 95% confidence intervals with the Finetti program.³² We constructed haplotypes with the PM program (version 1.0) and assessed differences in haplotype distributions with the Clump program (version 1.6), which determines an empirical p value by using the Monte Carlo method and 10 000 simulations.^{33–34} We performed power calculations with the G*Power program.³⁵ Significance level was set at $p < 0.05$.

RESULTS

We examined the seven single nucleotide polymorphisms individually in the groups of patients with schizophrenia and controls. Of the seven single nucleotide polymorphisms, five (*rs3211255*, *rs1062659*, *rs1062660*, *rs2957*, and *rs3173126*) in our samples were homozygous with AA, AA, AA, TT, and CC, respectively. In contrast, only two single nucleotide polymorphisms—*rs15982* (located in the 3' flanking region) and *rs4832* (located in exon 12)—had minor allele frequencies >30% and thus were chosen for further analysis.

Fisher's exact test found no significant deviation from the Hardy-Weinberg equilibrium was found in controls or cases for genotypes ($p = 0.91$ and $p = 0.54$ for *rs4832*, respectively, and $p = 0.74$ and $p = 0.51$ for *rs15982*, respectively) (table 1). In comparison with allelic and genotypic distributions of these two single nucleotide polymorphisms, we found no significant differences in the frequencies of A and C alleles and frequencies of AC or AA genotypes at *rs4832*, but we did

Table 1 Frequencies of alleles and genotypes of two common single nucleotide polymorphism loci of T complex protein 1 gene in patients with schizophrenia and healthy controls in the Chinese Han population. Values are numbers (frequencies) unless otherwise specified

Single nucleotide polymorphism										
Variable	rs4832					rs15982				
	Cases (n = 380)	Controls (n = 322)	Odds ratio (95% CI)	χ^2	p Value	Cases (n = 380)	Controls (n = 322)	Odds ratio (95% CI)	χ^2	p Value
Allele										
A	413 (0.54)	358 (0.56)	0.95 (0.77 to 1.17)	0.22	0.64	481 (0.63)	345 (0.54)	1.50 (1.21 to 1.85)	13.59	0.00023
C	347 (0.46)	286 (0.44)	1.00							
T						279 (0.37)	299 (0.46)	1.00		
p Value	0.54	0.91								
Genotype										
AA	109 (0.29)	100 (0.31)	0.92 (0.60 to 1.41)	0.15	0.70					
AC	195 (0.51)	158 (0.49)	1.04 (0.70 to 1.54)	0.04	0.85					
CC	76 (0.20)	64 (0.20)	1.00			149 (0.39)	94 (0.29)	2.35 (1.50 to 3.67)	14.18	0.00017
CT						183 (0.48)	157 (0.49)	1.72 (1.13 to 2.63)	6.41	0.011
TT						48 (0.13)	71 (0.22)	1.00		
p Value						0.51	0.74			

see significant differences in the frequencies of C and T alleles and CT and CC genotypes at rs15982 in the case and control groups (table 1).

We constructed four sets of haplotypes, which were derived from various combinations of alleles of the two single nucleotide polymorphisms (table 2). An estimate of haplotype frequencies showed significant differences between cases and controls by CLUMP program (version 1.6).

For power calculation with G*Power program based on Cohen’s method,³⁶ the sample size showed >60% power for genotype and >80% power for allele and haplotype to detect a significant ($\alpha<0.05$) association when an effect size index of 0.1, corresponding to a “weak” gene effect, was used. When an effect size index of 0.2, which corresponded to a “weak to moderate” gene effect was used, the sample size showed >90% power to detect significance ($\alpha<0.05$) in the association with allele, genotype, and haplotype.

DISCUSSION

We examined the association between two common single nucleotide polymorphisms in the *TCPI* gene on chromosome 6q and the risk of schizophrenia. A significant association with rs15982 was found. The frequency of the C allele of rs15982 was significantly higher in patients with schizophrenia compared with healthy controls. The single nucleotide polymorphisms rs15982 is located in the 3’ flanking region of the *TCPI* gene. From the Genome database (<http://www.ifti.org/TFsitescan>), we found a putative binding site for Myb or c-Myb in the 3’ flanking region of the *TCPI* gene. The DNA sequences recognised by c-Myb or Myb have been reported to contain the TAACGG sequence.^{25–26} Interestingly, the letter “A” in the TAACGG sequence was just the locus of rs15982. The c-Myb, or Myb functions as a transcriptional

activator that displays sequence specific DNA binding.^{23–26} Hence, it might be possible that when the letter “A” is replaced by “C” in the Myb or c-Myb binding target sequence, it results in an increase in the efficiency of transcription. Although this hypothesis can be used to explain the higher expression of TCPI in the hippocampal tissue of patients with schizophrenia, this needs to be confirmed further. These data, however, support the C allele of rs15982 as one risk factor for the development of schizophrenia. Haplotype analysis showed that the CC haplotype was more prevalent in cases than in controls, which suggests it also is associated with schizophrenia. To our knowledge, no association has been reported between schizophrenia and genetic variations in the *TCPI* gene, which resides within the linkage peak areas on 6q25.3–26. Additional genetic and functional studies are needed to further elucidate the function of this rs15982 locus polymorphism, but our data suggest that the *TCPI* gene may be involved in the aetiology of schizophrenia.

Some other genes may be related to schizophrenia; for example, the *DBI* (located on 2q) and *Mn SOD* (located on 6q), whose protein expressions were lower in the hippocampal tissue of patients with schizophrenia than in healthy controls. Diazepam binding inhibitor gene can downregulate the action of γ aminobutyric acid (GABA) by binding to the benzodiazepine recognition site located on the GABA_A receptor.³⁷ Manganese superoxide dismutase catalyses the dismutation of two molecules of peroxide radical to dioxygen and hydrogen in the mitochondria, which provides antioxidant defence against lipid peroxidation. The combined effect of *TCPI*, diazepam binding inhibitor gene and manganese superoxide dismutase may play an important role in the pathogenesis of schizophrenia. To understand the aetiology

Table 2 Frequencies of haplotypes of two common single nucleotide polymorphism loci of T complex protein 1 gene in patients with schizophrenia and healthy controls in the Chinese Han population. Values are numbers (frequencies) unless otherwise specified

Variable	Haplotype frequency				χ^2 test	Degrees of freedom	p Value
	AC	AT	CC	CT			
Cases	170 (0.22)	244 (0.32)	312 (0.41)	34 (0.05)	29.07	3	0.000002*
Controls	130 (0.20)	230 (0.36)	212 (0.33)	72 (0.11)	22.46	1	0.000002†

*T1 test.

†T4 test.

Electronic database information

- Online Mendelian Inheritance in Man (OMIM) (<http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?181500>)
- Genome database (<http://www.ncbi.nlm.nih.gov/SNP/> for selection of single nucleotide polymorphisms and <http://www.ifti.org/TFsitescan/> for putative transcriptional factors binding sites)

of complex diseases, we should study the interactions of gene–gene, protein–protein, and genetics–environment.

We may have found the real association between the *TCP1* gene and schizophrenia. We obtained a significant association with allele, genotype at the *rs15982* locus, and haplotype of two single nucleotide polymorphism loci (*rs4832* and *rs15982*). The *TCP1* gene is a positional candidate gene for schizophrenia based on linkage mapping data. The higher expression of *TCP1* in the hippocampal tissue of patients with schizophrenia may indicate its biological relevance to schizophrenia through affected neurotransmitter trafficking.^{20–21} Yaffe *et al* and Ursic *et al* found that *TCP1* plays a role in the folding of actin and tubulin, both of which are important for cytoskeletal maintenance.^{18–19} The *rs15982* locus polymorphism, which showed a strong association with schizophrenia, seems to be functional, as *rs15982* is just found in the DNA sequences recognised by the transcriptional factor of c-Myb or Myb. Our sample size had >90% power to detect a “weak to moderate” gene effect.

Conclusion

We found two common single nucleotide polymorphisms in the *TCP1* gene that show an association between the *TCP1* gene and schizophrenia and also support the idea of “common disease with common variant.” The results also are consistent with the conclusion of Edgar *et al*.¹⁶ The *TCP1* gene is likely a good candidate for functional study in the near future after further validation.

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