Molecular Psychiatry (2003) 8, 145–147

www.nature.com/mp

SCIENTIFIC CORRESPONDENCE

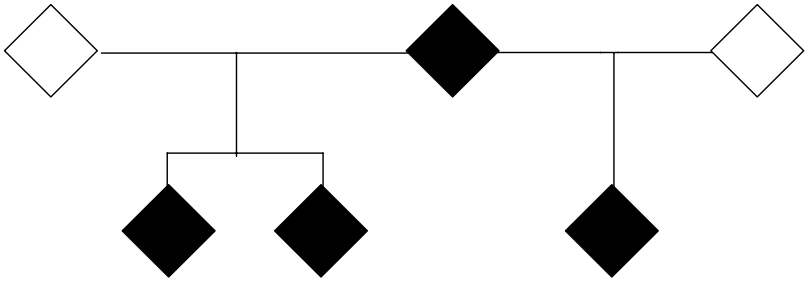
Recombination in a schizophrenic proband fails to exclude CHRNA7 at chromosome 15q14

Molecular Psychiatry (2003) **8**, 145–146. doi:10.1038/sj.mp.4001209

SIR – Meyer *et al*[1] conclude that *CHRNA7*, the gene that codes for the α7-nicotinic acetylcholine receptor, is excluded as a possible candidate gene in their extended pedigree of periodic catatonia, a subtype of schizophrenia. A recombination in one branch of their pedigree appears to exclude the region centromeric of D15S144 that includes *CHRNA7*. Mapping of disease loci based on a single recombination is a classic technique that is highly informative for many Mendelian traits, in which the assumption is that only a single rare allele accounts for the inheritance of the illness, but its value for complex, multigenic traits is less certain. Schizophrenia is assuredly such a multigenic trait;[2] even the periodic catatonia subtype is likely to be genetically heterogeneous, based on Meyer *et al's* finding that the linkage at 15q13–22 is largely accounted for by only a single family, with the remainder of their families having little evidence for linkage at any locus. The recombinant individual is one of two unaffected parents of a branch of the pedigree, so that the actual source of entry of the disease into this branch is uncertain. Indeed, all the three affected siblings in the branch share the same 15q13–22 haplotype from the other parent who has married into the extended pedigree, who is therefore also a possible source of the disease mutation.

A more informative pedigree in the NIMH Schizophrenia Genetics Initiative has a recombination in a schizophrenic proband that includes *CHRNA7*, and excludes D15S144 and more telomeric markers, the region that appeared to be included in the Meyer *et al* pedigree (Figure 1). In the NIMH pedigree, the half siblings are descended from an affected parent, and there is no other shared haplotype. The NIMH Genetics Initiative ascertainment rules did not allow pedigree extension through unaffected family members, to obviate the ambiguity found in the Meyer *et al* pedigree. D15S165, the most polymorphic marker near *CHRNA7*, shows significant transmission disequilibrium with schizophrenia in the NIMH families ($P = 0.0069$) and allele 6 is specifically transmitted in African-American families ($P = 0.0077$), such as the one shown in Figure 1.[3]

It is certainly possible that the Meyer *et al* and the NIMH pedigrees transmit schizophrenia by different genes in the 15q13–22 region or have cryptic recombinations that obscure genetic mapping or that either or both pedigrees have multiple entry of disease alleles from this or other loci. Thus, it would



Subject	*001*	*002*	*003*	*004*
D15S165	**6** 1	**6** 1	**6** 3	**6** 14
CHRNA7	**2** 2	**2** 3	**2** 3	**2** 3
D15S144	**4** 4	7 6	**4** 7	**4** 3
ACTC	**2** 11	11 10	**2** 11	**2** 11
D15S659	**5** 10	10 5	**5** 10	**5** 7

Figure 1 Recombination in a pedigree from the NIMH Schizophrenia Genetics Initiative. Affected status is indicated by darkened symbols; subject numbers are shown below each affected individual with genotypes. The two unaffected parents were not available for genotyping. Subjects 001, 002, 003 met DSMIIIR criteria for schizoaffective disorder, depressed type; subject 004 met criteria for schizophrenia. *CHRNA7* was genotyped by alleles of D15S1360, a dinucleotide repeat in the gene's second intron; although Meyer *et al* show both *CHRNA7* and *CHRNA7dup* telomeric of D15S165, physical mapping in BAC and YAC contigs place *CHRNA7dup* centromeric of D15S165 and *CHRNA7* telomeric.[4,5] Diagnostic and genotyping procedures were previously described.[3]

seem premature in a common, multigenic illness to claim exclusion of any locus based on a single recombination, particularly one that occurs in an unaffected individual.

S Leonard and R Freedman
Departments of Psychiatry and Pharmacology, Denver VA Medical Center and University of Colorado Health Sciences Center, 4200 East Ninth Avenue C-268-71, Denver, CO 80262, USA

Correspondence should be addressed to R Freedman.
E-mail: Robert.Freedman@UCHSC.edu

1 Meyer J *et al. Mol Psychiatry* 2002; **7**: 220–223.
2 Baron M. *Am J Hum Gen* 2001; **68**: 299–312.
3 Freedman R *et al. Am J Med Gen (Neuropysch Gen)* 2001; **105**: 20–22.
4 Riley B, Williamson M, Collier D, Wilkie H, Makoff A. *Genomics* 2002; **79**: 197–209.
5 Gault J *et al. Genomics* 1998; **52**: 173–85.

Association between the BDNF gene and schizophrenia

Molecular Psychiatry (2003) **8**, 146–147. doi:10.1038/sj.mp.4001221

Converging lines of evidence suggest that the brain-derived neurotrophic factor (BDNF) could be implicated in the neurodevelopmental abnormalities found in schizophrenia brain.[1] BDNF is involved in a variety of trophic and neuromodulatory effects that include an important role in the development and survival of dopaminergic and serotonergic neurons. BDNF levels are increased in hippocampus and anterior cingulate cortex of schizophrenia brains,[2] a rat model of schizophrenia shows altered expression of the BDNF gene (*BDNF*), *BDNF* knock-out mice exhibit dysfunction of dopaminergic and serotonergic transmission, and neuroleptics appear to influence *BDNF* expression.[3] *BDNF* is expressed throughout life, and thus altered *BDNF* expression or modified protein structure determined by variations in the gene could have a cumulative effect and be at least partly responsible for the subtle anomalies described in schizophrenia brains.[1]

BDNF has been mapped to chromosome 11p13 and a $(GT)_n$ dinucleotide repeat is present 1.04 kb upstream from the transcription initiation site.[4] This polymorphism has been tested for association with schizophrenia in five independent studies.[5–9] Three of these studies[6–8] used a case–control association strategy, one[9] used a family-based approach, while the other study used both the family and the case–control approach.[5] None of these data sets showed association between the *BDNF* dinucleotide repeat and schizophrenia. However, Krebs *et al*[6] reported the presence of an association between a group of *BDNF* dinucleotide long alleles (172–176 bp) and late-onset schizophrenia patients who responded to neuroleptics. In the present study, we tested for association between the *BDNF* dinucleotide polymorphism and schizophrenia in a sample of nuclear families. The DNAs from 89 schizophrenia patients and both respective parents were available. The DNAs were extracted from lymphocytes of patients assessed at the Department of Neuropsychiatric Science of the San Raffaele Hospital in Milan, the Department of Clinical Psychiatry at the University of Rome, Italy, and at the Centre for Addiction and Mental Health, Clarke Site, an affiliated hospital of the University of Toronto, Canada. All patients were diagnosed according to DSM-III-R criteria, by at least two psychiatrists, following administration of the Diagnostic Interview Schedule for the Italian sample and of the Structured Clinical Interview for DSM (SCID) in the Canadian sample. The dinucleotide polymorphism was genotyped using the method originally described by Proschel *et al*.[4] We analyzed our families for the presence of association using the transmission disequilibrium test for multiallelic polymorphisms as in ETDT (v1.8). The ETDT allele-wise and genotype-wise analyses showed biased transmissions of the *BDNF* $(GT)_n$ alleles from the parents to the schizophrenia probands (allele-wise $\chi^2 = 7.9$, 3 df, $P = 0.04$; genotype-wise $\chi^2 = 12.2$, 6 df, $P = 0.05$, and empirical P values via Monte Carlo ETDT: allele-wise $P = 0.04$; genotype-wise $P = 0.08$, single allele $P = 0.02$). The analysis of transmissions of the individual alleles (see Table 1) showed that allele 3 (170 bp) was more often transmitted (42 times) to the probands than non-transmitted (21 times). The same pattern of biased transmissions was observed when the data set was subdivided according to the two ethno-cultural groups present in our sample. Allele 3 showed 28 transmissions *vs* 15 nontransmissions in the Canadian families who were primarily of northern European ancestry, while the Italians showed 14 transmissions *vs* six nontransmissions. The analysis of the allele transmissions stratified for the parents' sex showed a parent of origin effect (POE) since preferential transmissions of allele 3 derived from the

Table 1 ETDT analysis for individual alleles of the *BDNF* $(GT)_n$ polymorphism in 89 triad families of schizophrenia probands

	A1[a] (174 bp)	A2 (172 bp)	A3[b] (170 bp)	A4 (168 bp)
Transmission	16	3	42	8
Non-Transmission	34	5	21	9

[a]$\chi^2 = 6.48$; 1 df; $P = 0.010$.
[b]$\chi^2 = 7.0$; 1 df; $P = 0.0081$.

maternal meiosis were observed (maternal 21 transmissions *vs* six nontransmissions, $P = 0.003$; paternal 16 transmissions *vs* 10 nontransmissions, $P = 0.2$).

Our sample showed modest evidence for an association between the 170 bp dinucleotide repeats *BDNF* allele and schizophrenia. The increase in the number of transmissions for the allele 3 continues to be marginally significant ($P = 0.03$) after Bonferroni correction for four multiple tests performed to analyze the transmissions of each allele independently. However, most previous studies did not show the presence of association. Several nonmutually exclusive factors can produce conflicting results in association studies of common complex diseases including the presence of genetic, clinical and population heterogeneity. One of the previous studies was conducted in Japanese patients,[7] one in Roscommon County in Ireland,[5] one in 48 triads from Iowa,[9] and one in Spanish Caucasians.[8] The study by Krebs *et al*[6] showed evidence for association between a group of *BDNF* dinucleotide alleles (ranging from 172 to 176 bp) and a small sample of French Caucasian patients with late onset of the disease and good response to neuroleptics.[6] The association reported in this study could explain the apparently contrasting results between the present report and previous studies.

The POE we observed in the transmission of the BDNF allele could be due to a parent-specific expression of *BDNF*, named genomic imprinting. *BDNF* is located between two imprinted loci: ~24 Mb centromeric from the oxysterol binding protein homologue 1 gene (*OBPH1*) on 11p15.5 and ~4 Mb telomeric from Wilson tumor 1 gene (*WT1*) on 11p13, a brain expressed zinc finger protein maternally expressed in the brain.[10] However, the presence of imprinting has never been demonstrated for *BDNF* thus far.

The functions of BDNF described are strongly supportive of a role of this neurotrophin in processes that may be disrupted in schizophrenia.[1] A sustained qualitative or quantitative abnormality in the synthesis of BDNF determined by a defective gene could be involved in the anomalies described in post-mortem studies of schizophrenic brains. Furthermore, a defective *BDNF* could determine an altered BDNF synthesis in response to numerous environmental factors that have a demonstrated ability to modify *BDNF* expression.

In conclusion, a role for *BDNF* as a predisposing gene for schizophrenia is suggested by our result; however, its meaning in the context of several other negative studies requires further evaluation. The GT polymorphism is in proximity of the *BDNF* promoter region. A direct functional role of the repeat is needed considering the numerous lines of evidence showing the function of VNTRs in non-coding regions as transcriptional activating elements.[11] Furthermore, several regulatory elements within *BDNF* have been described[12] and the presence of linkage disequilibrium between the GT repeat and polymorphisms in these regions need also to be addressed.

P Muglia[1], AM Vicente[2], M Verga[1], N King[1], F Macciardi[1] and JL Kennedy[1]

[1]*Department of Psychiatry, Neurogenetics Section, Centre for Addiction and Mental Health, University of Toronto, 250 College street R-30, Toronto, Ontaria Canada M5T 1R8;* [2]*Instituto Gulbenkian de Ciência, Oeiras, Portugal*

Correspondence should be addressed to JL Kennedy.
E-mail: James_Kennedy@camh.net

1 Nawa H, Takahashi M, Patterson PH. *Mol Psychiatry* 2000; **5**: 594–603.
2 Takahashi M, *et al. Mol Psychiatry* 2000; **5**: 293–300.
3 Lipska BK, Khaing ZZ, Weickert CS, Weinberger DR. *Eur J Neurosci* 2001; **14**: 135–144.
4 Proschel M, Saunders A, Roses AD, Muller CR. *Hum Mol Genet* 1992; **1**: 353.
5 Hawi Z, Straub RE, O'Neill A, Kendler KS, Walsh D, Gill M. *Psychiatry Res* 1998; **81**: 111–116.
6 Krebs MO *et al. Mol Psychiatry* 2000; **5**: 558–562.
7 Sasaki T *et al. Am J Med Genet* 1997; **74**: 443–444.
8 Virgos C *et al. Schizophr Res* 2001; **49**: 65–71.
9 Wassink TH, Nelson JJ, Crowe RR. *Am J Med Genet* 1999; **88**: 724–728.
10 Morison IM, Reeve AE. *Hum Mol Genet* 1998; **7**: 1599–1609.
11 Kashi Y, King D, Soller M. *Trends Genet* 1997; **13**: 74–78.
12 Tao X, West AE, Chen WG, Corfas G, Greenberg ME. *Neuron* 2002; **33**: 383–395.