Psychiatric Genetics 1999; **9**:1–6

Lack of genetic linkage or association between a functional serotonin transporter polymorphism and panic disorder

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Received 8 September 1998; accepted 2 December 1998

Given the efficacy of medications that interact with the serotonin transporter (5-HTT) in the treatment of panic disorder, we have used a family-based design to test for genetic association and linkage between panic disorder and a functional polymorphism in the promoter of the gene for 5-HTT. In this study, 340 individuals in 45 families, as well as 74 haplotype relative risk 'trios' were genotyped at the polymorphic locus, which consists of a 44 base pair deletion/insertion. There were no significant differences in allele frequencies or occurrence of genotypes within the triads. No linkage between the 5-HTT polymorphism and panic disorder was observed in the multiplex families, using a variety of simulations for dominant and recessive models of inheritance. Recent reports suggest an association between the 5-HTT polymorphism and anxiety-related traits, as measured with personality assessment. The results reported here provide evidence that the genetic basis of panic disorder may be distinct from anxiety-related traits assessed by personality inventories in normal populations.

Keywords: panic disorder, serotonin transporter, association study, linkage study, candidate gene

INTRODUCTION

Panic disorder is a well-characterized anxiety syndrome, in which somatic symptoms, such as palpitations, dyspnea, and dizziness, are coupled with severe anxiety, including fears of going crazy or dying. There is evidence that panic disorder is familial (Knowles and Weissman, 1995), particularly in persons with early onset (Goldstein *et al.*, 1997). Lifetime prevalence is between 1 and 3% cross-nationally (Weissman *et al.*, 1997). One exception is Taiwan, where the rate of panic disorder, and of most other psychiatric conditions, is reported to be low. The clinical presentation and average age of onset, however, remains similar across divergent cultures. Investigation into the biological basis of the disorder has been centered on physiological parameters, such as lactate infusion, *m*-chlorophenylpiperazine infusion, cholecystokinin infusion, and tryptophan depletion, as well as differential response to medications. Medications that are thought to interact with serotonergic systems, such as monoamine oxidase A inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs), have proven efficacious in treating panic disorder. This suggests a potential role in panic disorder for proteins involved in serotonin (5-HT) synthesis, transport, or catabolism.

A number of studies have recently focused on the gene (SLC6A4) for one protein involved in serotonergic neurotransmission, the serotonin transporter (5-HTT) on chromosome 17q11.1-q12. A polymorphism in the promoter region of the gene has been identified (5-HTTLPR), consisting of a 44 base pair insertion/deletion, approximately one kilobase upstream of the transcriptional start site. Transfection studies in human cell lines demonstrated that the longer variant of the promoter was more efficiently transcribed (Heils *et al.*, 1996). Studies of native 5-HTT function showed reduction in gene transcription and serotonin reuptake in cell lines containing the shorter promoter variant (Lesch *et al.*, 1996).

A number of groups have examined the relationship of this functional promoter polymorphism to anxiety trait and/or disorders. In the first such study, the short allele was found to be associated with anxiety-related traits (as measured by the NEO personality inventory and the 16PF personality inventory, and indirectly by extrapolating the Tridimensional Personality Questionnaire (TPQ) scores from the NEO data) in 505 normal individuals. This locus was estimated to account for 7–9% of the total genetic variance in anxiety-related personality traits (Lesch *et al.*, 1996). Replication of the association for harm avoidance, assessed with the TPQ, has been observed in one study of 84 elderly persons (47 with Parkinson's disease and 37 controls) (Ricketts *et al.*, 1998), while two subdimensions of harm avoidance showed positive linkage to transporter polymorphism in a sib pair analysis of alcoholic violent offenders (Mazzanti *et al.*, 1998). The association was not replicated in a study of 203 normal Japanese females assessed with an extended version of the TPQ (Nakamura *et al.*, 1997), or in a study of 120 normal Israelis assessed with the TPQ (Ebstein *et al.*, 1997).

Three recent reports have documented an absence of association between DSM-III-R/DSM-IV panic disorder and 5-HTT promoter polymorphism in Japanese, German, and Italian patients when compared to healthy, unrelated controls (Deckert *et al.*, 1997; Ishiguro *et al.*, 1997; Matsushita *et al.*, 1997). In this report, we use a family-based study design to analyze a large collection of multiplex panic disorder pedigrees and haplotype relative risk 'triads' for genetic linkage and/or association between the promoter polymorphism of the 5-HTT and panic disorder.

METHODS

Subjects

Families were recruited from several sources, including anxiety clinics, therapists specializing in treating anxiety disorders, and anxiety disorder support groups/associations. Families with at least three affected persons were asked to participate, and all 45 families in this report had at least three affected individuals when the pedigrees were complete. Participants underwent interviews, utilizing the Schedule for Affective Disorders and Schizophrenia-Lifetime Version for Anxiety Disorders, Revised (Mannuzza *et al.*, 1986), and the Family Informant Schedule and Criteria (Mannuzza *et al.*, 1985), from which DSM-III-R diagnoses of panic disorder with recurrent spontaneous panic attack ± agoraphobia (APA) were derived, as previously described (Knowles *et al.*, 1998; Fyer and Weissman, 1998). 340 individuals in 45 multiplex families and 225 individuals in 74 triads consisting of proband, mother and father, were genotyped. Twenty-nine of the triads were ascertained from the 45 linkage families. Of these, 21 triads had a single affected parent using definite and probable criteria, while if possible/any criteria were used, four additional triads had one affected parent, and four triads had two affected parents. Twenty-three triads were obtained from linkage families in progress that were not genotyped in this report. Eleven of these triads had one affected parent using definite/probable criteria, and three additional triads had a single affected parent while two triads had two affected parents if possible/any criteria were used. The remaining 22 triads were culled from family and association studies of panic disorder, or recruited, but not used in the linkage study. Parental affected status is unknown for these triads.

DNA Analysis

Preparation of the DNA samples was as described elsewhere (Knowles *et al.*, 1998). Polymerase chain reaction (PCR) was performed using a modification (Edenberg and Reynolds, 1998) of an earlier method (Lesch *et al.*, 1996). Briefly, PCR reactions of 15 microliters (μl) containing 10 pmols of the forward and reverse primers (stpr5, 5-GGCCTTGCCG-CTCTGAATTGC-3, and stpr3, 5-GAGGGACT-GAGCTGGACAACCCAC-3), 100 ng DNA template, 200μM dNTPs (dTTP, dATP, dCTP), 100 μM dGTP, 100 μM 7-deaza-2-dGTP, 50 mM KCl, 10 mM Tris-HCl (pH 8.3 at 37°C), 1.83 mM $MgCl_2$, and 1 unit regular Taq polymerase, were cycled at 95°C for 5 min, followed by 45 cycles of 95°C for 30 s, 61°C for 30 s, and 72°C for 60 s, on a MJ Research PTC-200 Thermal Cycler in 96-well plates. Gelatin was left out of protocol. PCR products were separated by electrophoresing 6 μl aliquots on a 2.5% agarose gel infiltrated with ethidium bromide, and expected products of 528 and 484 base pairs were visualized with UV light.

Data Analysis

Pedigrees were analyzed for linkage, using both dominant and recessive genetic models of inheritance and a penetrance of 50%, as well as SIBPAIR, under three diagnostic models (narrow, intermediate, and broad) using the ANALYSE package (Terwilliger, 1994). In the 'narrow' model, individuals who are diagnosed as having 'definite' or 'probable' panic disorder are coded as affected (Knowles *et al.*, 1998).

TABLE 1. Linkage analyses of multiplex families with 5-HTTLPR

Dx model[a]	Genetic model	$Z_{max,\ \theta}$	$Z_{max\text{-}Het,\ \theta,\ \alpha}$	SIBPAIR
Narrow	Dominant	0.00, 0.50	0.05, 0.00, 0.08	0.54
Narrow	Recessive	0.27, 0.24	0.30, 0.10, 0.44	
Intermediate	Dominant	0.00, 0.50	0.01, 0.00, 0.03	0.77
Intermediate	Recessive	0.10, 0.32	0.18, 0.04, 0.22	
Broad	Dominant	0.00, 0.50	0.00, 0.50, 1.00	0.89
Broad	Recessive	0.01, 0.38	0.08, 0.00, 0.13	

[a]Dx model, diagnostic model.

The 'intermediate' model adds individuals diagnosed with 'possible; panic disorder, and the 'broad' model adds those with 'any' panic disorder. 'Possible' and 'any' panic disorder are defined as:

Possible – recurrent panic episodes with at least two symptoms. Frequency ≥ 4 in four weeks, accompanying avoidance and/or persistence fears are recorded but not required.

Any – does not meet criteria for definite, probable or possible panic disorder, but has some sign or symptom of panic disorder, e.g. one single severe spontaneous panic, but no sequelae.

Alleles in the 'triad' families were analyzed with the haplotype relative risk (HRR) method (Falk and Rubinstein, 1987; Terwilliger and Ott, 1992), and the transmission disequilibrium test (TDT) statistic (Spielman *et al.*, 1993), while genotype analyses were performed with contingency table χ^2 tests. Simulation analyses were performed using SLINK (Ott, 1989; Weeks *et al.*, 1990).

RESULTS

The frequency of the longer allele (*l*) in the 74 triad probands was 64.9%, with 35.1% frequency of the shorter allele (*s*). Genotype frequencies were 46.0% *l/l*, 37.8% *l/s*, and 16.2% *s/s*. This was not significantly outside of Hardy–Weinberg equilibrium ($\chi^2_1 = 2.12$, n.s. = not significant). For the 99 genetically independent subjects used to calculate allele frequencies within the pedigrees, the frequency of the *l* allele was 65.2%, with 34.8% *s* allele. The genotype frequencies were 45.5% *l/l*, 39.4% *l/s*, and 15.1% *s/s*. These frequencies are also within Hardy–Weinberg equilibrium ($\chi^2_1 = 1.73$, n.s.).

A summary of the LOD score linkage analysis of the multiplex families is presented in Table 1. The highest LOD score observed was 0.89, with the broad diagnostic model using the SIBPAIR statistic. Scores for the dominant and recessive analyses under the assumption of genetic homo- or heterogeneity were all essentially negative at low recombination fractions. To determine the power to detect linkage given our collection of pedigrees, we carried out a series of simulation analyses using SLINK (Ott, 1989; Weeks *et al.*, 1990; Ott, 1989). These were performed for the broad, intermediate and narrow diagnostic models, under both dominant and recessive modes of inheritance. For each simulation run, 200 replicates were generated under both genetic homogeneity and heterogeneity, a recombination fraction ($\theta = 0.0$) between the 'disease' and the bi-allelic serotonin transporter gene with allele frequencies 0.652 and 0.348. For the dominant/recessive genetic models, and assuming genetic homogeneity, the maximum average LOD scores (ELODs) for the three diagnostic classifications were 5.99/6.34 (Broad), 6.16/5.93 (Intermediate) and 6.11/5.17 (Narrow). The ELODs for the range of heterogeneity models were proportionately lower (e.g., ELODs for Broad dominant model with $\alpha = 0.75, 0.5, 0.25$ are 4.92, 2.99, and 1.50, respectively).

When transmission of the alleles for the serotonin transporter was investigated in 74 triads consisting of both parents and a proband, no preferential transmission of either allele was observed using the HRR ($P = 0.40$) (Table 2). Of the 148 parents, 73 were heterozygous for the polymorphism, with 33 triads with one heterozygous parent and 20 triads with two heterozygous parents. Using the heterozygous parents, the TDT also found no preferential transmission of the serotonin transporter alleles ($P = 0.39$). Similarly, panic probands did not significantly differ from HRR 'controls', which are reconstituted from parental alleles, when examined by genotype (Table 3, $\chi^2_2 = 2.36$, n.s.).

It has been suggested that the polymorphism has more of a dominant-recessive than codominant-

TABLE 2. Frequency of 5-HTTLPR alleles in HRR triads[a]

Allele	Transmitted	Non-transmitted
Long	96	89
Short	52	59

[a]Haplotype relative risk, HRR ($P = 0.40$, n.s.).

TABLE 3. Frequency of 5-HTTLPR genotypes in HRR triads[a]

Genotype	Probands	'Controls'
l/l	34	26
l/s	28	37
s/s	12	11

[a]*l*, long allele. *s*, short allele. 'Controls' are genotypes constructed from non-transmitted alleles in each triad. $\chi^2_2 = 2.36$, 2df, n.s.

additive effect, given that the expression of the gene in cell lines derived from individuals with the *s/s* or *s/l* genotype is similar, and differs from those with the *l/l* genotype (Lesch *et al.*, 1996). We tested whether the genotypic distribution of the probands in triads when grouped this way was different from that of the 'control' genotypes re-constructed from the parents (Table 4). There was a slight excess of genotypes containing the short allele in the control group ($\chi^2_1 = 1.79$, n.s.), the opposite of the predicted outcome if the short allele predisposes individuals to panic disorder.

Panic disorder is about twice as frequent in females as males in the general population (Weissman *et al.*, 1997). Given this observed sex effect, and the observation of a potential sex-specific genetic association in another anxiety disorder (Karayiorgou *et al.*, 1997), we examined this dominant-recessive model when the triads were stratified by the sex of the proband (Table 5). Among female probands, there was an excess of control genotypes containing the short allele, again contrary to the hypothesis that the shorter allele would contribute to panic disorder ($\chi^2_1 = 4.55$, $P = 0.03$). This relationship was not noted with male probands.

DISCUSSION

The results presented here do not support the hypothesis that this promoter polymorphism in the 5-HTT gene accounts for a significant portion of the genetic variance to develop panic disorder. These

TABLE 4. Frequency of normal (*l/l*) *vs* low-activity (*l/s* + *s/s*) genotypes in HRR triads[a]

Genotype	Probands	'Controls'
l/l	34	26
l/s + *s/s*	40	48

[a]*l*, long allele. *s*, short allele. 'Controls' are genotypes constructed from non-transmitted alleles in each triad. Significance determined for *l/l vs l/s* or *s/s* genotypes, $\chi^2_1 = 1.79$, 1df, n.s.

TABLE 5. Frequency of normal (*l/l*) *vs* low-activity (*l/s* + *s/s*) genotypes by gender of proband in HRR triads

	Female		Male	
Genotype	Probands	'Controls'	Probands	'Controls'
l/l	28	17	6	9
l/s + *s/s*	27	38	13	10

Significance determined for *l/l* vs *l/s* or *s/s* genotypes by female gender, $\chi^2_1 = 4.55$, 1df, $P = 0.03$. By male gender, $\chi^2_1 = 0.991$, 1df, n.s.

data are in agreement with three recent reports, in which persons with panic disorder did not differ from control populations with respect to the frequency of 5-HTT promoter variants (Deckert *et al.*, 1997; Ishiguro *et al.*, 1997; Matsushita *et al.*, 1997). The present study extends these studies by utilizing a sample of 'triad' families for association analyses, and by examination of linkage of the polymorphism in 45 multiplex pedigrees segregating panic disorder. We observed no evidence for linkage in the multiplex pedigree sample, even though simulations indicate that this sample should have sufficient power to detect linkage with a biallelic marker for a homogenous disease. In addition, no evidence for preferential transmission of the short allele was observed in the 'triad' families. Linkage disequilibrium between the *long* promoter allele and OCD has been observed in a recent triad-based study of the polymorphism in obsessive–compulsive disorder (OCD) (McDougle *et al.*, 1998). We observed a suggestion of an increased frequency of the *l/l* genotype, particularly in the female probands, but these results were not corrected for multiple testing. The lack of a significant sex effect is consistent with the results of Haghighi *et al.* (1998), who essentially found no evidence of 'parent-or-origin' effect in the transmission of panic disorder in families. Notably, we observed more homozygosity (*l/l* or *s/s*) among the triad probands (Table 3), but this finding was not statistically significant. This finding was also found in a population-based study of OCD, in which a trend towards homozygosity existed in patients when compared to normal unrelated controls (Billet *et al.*, 1997).

Beyond panic disorder and anxiety-related traits, a growing literature exists which claims to observe genetic association between the 5-HTTLPR promoter polymorphism and various psychopathologies, including depression, autism, alcohol dependence, Alzheimer's disease, and seasonality. Collier *et al.* reported that the shorter 5-HTTLPR allele occurs more frequently in patients with unipolar and bipolar affective disorders, as well as an excess of the *s/s*

genotype ($P = 0.03$, 0.02, respectively) (Collier *et al.*, 1996). A smaller study failed to replicate this finding (Furlong *et al.*, 1998). A family-based design was used to detect a preferential transmission ($P = 0.03$) of the shorter allele in 86 triads with a proband with autistic disorder (Cook *et al.*, 1997). A population-based study was used by Sander *et al.* to study 103 severe alcoholics, who were found to have significantly higher frequencies of the shorter allele and the *s/s* genotype ($P = 0.049$, 0.035, respectively; Sander *et al.*, 1997). Similarly, 196 persons with Alzheimer's disease were found to have higher frequencies of the shorter allele and the *s/s* genotype ($P = 0.004$, 0.03, respectively) when compared to unrelated controls (Li *et al.*, 1997). Rosenthal *et al.* studied 97 patients with seasonal affective disorder (SAD), comparing them to 71 unrelated controls. SAD patients were more likely to have the shorter 5-HTTLPR allele, and were also more likely to have the *l/s* or *s/s* genotype ($P < 0.02$, 0.01, respectively; Rosenthal *et al.*, 1998). Patients with the shorter allele had significantly higher scores on a instrument measuring seasonality.

This study represents the first analysis of association between the 5-HTTLPR promoter polymorphism and panic disorder using a family-based design. Family-based association studies reduce artifacts of allelic frequency variation, admixture, and ethnic confounding. Our negative association stands in contrast to two other association studies, which showed positive association between the 5-HTTLPR promoter variant and personality traits of neuroticism (Lesch *et al.*, 1996) and the uncertainty/anticipatory/worry subscales of TPQ harm avoidance (Mazzanti *et al.*, 1998) in the general population. The latter study is intriguing, given its use of 366 sib-pairs derived from 182 violent alcoholic offenders, 358 of their relatives, and 215 controls. If this functional promoter variant in the serotonin transporter gene does account for a portion of the genetic variation to anxiety trait, our findings argue against a continuum between DSM-III-R panic disorder and the traits of anxiety measured in non-pathological populations. The lack of a continuum is also supported by the absence of coincident positive linkage findings in genome scans for panic disorder and harm avoidance (Knowles *et al.*, 1998; Cloninger *et al.*, 1998). Further, our findings would imply that panic disorder does not describe the same phenomenon as do the traits of neuroticism or harm avoidance. Genetic substrates may differ between the pathologic extremes, as opposed to more general dimensions of personality. Interestingly, Greenberg *et al.* cited an unpublished re-analysis of the study associating neuroticism and 5-HTTLPR promoter variant, and found that the polymorphism was associated least strongly with the extremes of neuroticism scores (Greenberg *et al.*, 1998).

Acknowledgments

The authors would like to acknowledge the invaluable contribution made by the families who participated in this study. This study was supported by grants: NIMH; MH28274 (MMW), MH37592 (AJF), MH30906 (DFK), and MH48858 (SEH).

Note: Diagnostic assessment of the 74 association triads revealed that one proband had panic disorder and concurrent major depression, while the remainder of the probands had only panic disorder.

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