American Journal of Medical Genetics (Neuropsychiatric Genetics) 114:626–630 (2002)

Aromatic Amino Acid Hydroxylase Genes and Schizophrenia

Helen M. Chao[1,2]* and Mary Ann Richardson[1,2]

[1]*The Nathan S. Kline Institute for Psychiatric Research, New York State Office of Mental Health, Orangeburg, New York*
[2]*New York University Medical Center, New York, New York*

Phenylalanine hydroxylase (PAH), which catalyzes the conversion of phenylalanine to tyrosine, shares physical, structural and catalytic properties with tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH) that catalyze the rate-limiting steps in the biosynthesis of the neurotransmitters dopamine, noradrenaline, and serotonin. Because these neurotransmitter systems have all been implicated in the pathophysiology of schizophrenia, the aromatic amino acid hydroxylases are among the likely candidates for genes associated with schizophrenia. A mutation in the functionally critical tetrahydrobiopterin cofactor binding domain of the PAH gene had been identified in African-American patients with the diagnosis of schizophrenia, and biochemical analyses suggested that this mutation has physiological consequences related to amine neurotransmitter function. DNA sequencing of the highly conserved cofactor binding domain of the PAH, TH, and TPH genes in African-American subjects with schizophrenia and unrelated, never mentally ill subjects from the NIMH Schizophrenia Genetics Initiative, was undertaken to assess the concordance of mutant genotype with psychiatric phenotype. The K274E mutation was observed in the PAH gene cofactor binding domain, and several polymorphisms were identified in adjacent intronic regions of the PAH, TH, and TPH genes. All of the genetic variants observed were represented in the schizophrenia group and in the never mentally ill group. Genetic evaluation of the family members of subjects with the PAH K274E mutation showed that all individuals with the K274E mutation also exhibited the PAH L321L polymorphism in the catalytic domain of the PAH enzyme.

KEY WORDS: phenylalanine; tyrosine; tryptophan; tetrahydrobiopterin

INTRODUCTION

Phenylalanine hydroxylase (PAH) catalyzes the conversion of phenylalanine to tyrosine, the rate limiting step in the catabolism of phenylalanine. Tyrosine hydroxylase (TH) catalyzes the hydroxylation of tyrosine to L-dopa, the rate-limiting step in the synthesis of catecholamines such as dopamine and noradrenaline, and tryptophan hydroxylase (TPH) catalyzes the rate-limiting step in the biosynthesis of serotonin. The dopamine, noradrenaline and serotonin neurotransmitter systems have all been implicated in the pathophysiology of schizophrenia [Van Kammen and Kelley, 1991; Joyce, 1993; Lieberman et al., 1998].

The aromatic amino acid hydroxylases share physical, structural, and catalytic properties. All three enzymes require the reduced pterin tetrahydrobiopterin as cofactor, as well as molecular oxygen and iron, to hydroxylate their amino acid substrate [Hufton et al., 1995]. Structure/function analyses have identified a central catalytic domain that contains sites for substrate, iron, and cofactor binding, an N-terminal region with regulatory properties, and a C-terminal domain involved with intersubunit binding [Hufton et al., 1995; Waters et al., 1998]. The human PAH, TH, and TPH genes show a high degree of sequence homology with the most conserved region of 340 amino acids localized in the catalytic domain. This region has a 49% sequence identity among the hydroxylases without any gaps and with mostly conservative substitutions [Boularand et al., 1995]. Localization of the human TPH gene near the TH locus, and the level of sequence conservation, suggest that the three enzymes are members of a gene superfamily [Ledley et al., 1987].

The PAH gene was screened for sequence variants in psychiatric patients to test the hypothesis that PAH

Grant sponsor: NIMH; Grant number: MH62352-01.

*Correspondence to: Helen M. Chao, Ph.D., The Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Bldg. 35, Orangeburg, NY 10962. E-mail: chaoh@nki.rfmh.org

Received 4 January 2002; Accepted 17 April 2002

DOI 10.1002/ajmg.10606)

mutation, by altering phenylalanine metabolism, could have long-term effects including predisposition to psychiatric disorders [Richardson et al., 1999a,b]. The genetic analysis identified in four patients, all with the diagnosis of schizophrenia, the K274E mutation, a lysine to glutamic acid substitution at amino acid 274 in the cofactor binding domain. The K274E mutation was observed only in African-American subjects, although this ethnic group composed about one-third of the patient group. Biochemical analyses further indicated that in patients with the K274E mutation, there were alterations in phenylalanine kinetics and tetrahydrobiopterin cofactor synthesis consistent with chronically increased plasma phenylalanine and availability of phenylalanine to the brain. Elevated plasma phenylalanine could reduce brain availability of tyrosine and tryptophan because these amino acids compete for transport across the blood-brain barrier [Pardridge and Choi, 1986] and thereby result in reduced dopamine, noradrenaline and serotonin biosynthesis.

The results of analyses of TH and TPH for association of genetic polymorphisms with psychiatric disorder have been varied. A rare microsatellite allele in intron 1 (IVS1) of the TH gene was reported to be associated with schizophrenia in studies of British, French, and Tunisian cohorts [Meloni et al., 1995; Wei et al., 1995] but this finding was not replicated by investigations of Japanese [Ishiguro et al., 1998] and Swedish [Jonsson et al., 1998] subjects. The disparate results may be due to ethnic differences, as it has been suggested that genetic markers for schizophrenia may differ between ethnic groups [Cloninger et al., 1998]. Case-control analyses for the T-229A, V81M and V468M variants showed no evidence for association between these TH polymorphisms and schizophrenia [Ishiguro et al., 1998; Kunugi et al., 1998]. A report of a positive association between the TPH IVS7 A218C allele and bipolar disorder [Bellivier et al., 1998] was not confirmed by other studies [Furlong et al., 1998; Kirov et al., 1999; McQuillin et al., 1999], and the results from testing this polymorphism for association with unipolar depressive disorder were negative [Furlong et al., 1998; Frisch et al., 1999]. The TPH IVS7 A779C allele has been reported to be related to aggressive behavior in schizophrenia and schizoaffective disorder [New et al., 1998; Nolan et al., 2000], to negative symptoms in male patients with schizophrenia [Shinkai et al., 2000], and to suicidal behavior in some studies [Nielsen et al., 1994, 1998] but not in others [Kunugi et al., 1999; Bennett et al., 2000].

The identification of the PAH K274E mutation in patients with schizophrenia suggested that mutations in the structurally and functionally homologous tetrahydrobiopterin cofactor binding regions of all three aromatic amino acid hydroxylase genes may be observed in subjects with schizophrenia. Based on the previous observation of the PAH K274E mutation only in subjects of African-American ethnicity, the present study focused on subjects of this ethnic group. The NIMH Schizophrenia Genetics Initiative was established as a national resource of clinical data and genomic DNA for the study of schizophrenia [Cloninger et al., 1998]. Demographic and clinical information has been collected for all of the subjects for whom DNA is available, and this database served as the source for the genomic DNA analyzed in the present study.

MATERIALS AND METHODS

The psychiatric evaluation categories delineated by the NIMH Schizophrenia Genetics Initiative [Cloninger et al., 1998] are: 1) DSM-III-R schizophrenia; 2) DSM-III-R schizoaffective disorder-depressive type (SA); 3) DSM-III-R schizotypal personality disorder (schizophreniform disorder, delusional disorder, psychotic disorder NOS), or mood-incongruent psychotic depressive disorder (ST); 4) DSM-III-R paranoid or schizoid personality disorder, mood-congruent or unspecified psychotic depressive disorder, or unknown psychotic disorder with or without hospitalization; 5) DSM-III-R schizoaffective disorder-bipolar type; 6) other mental disorder (OM); 7) never mentally ill; and 8) unknown (?). Genomic DNA for 41 African-American subjects with schizophrenia and for 17 African-American subjects who were identified as never mentally ill and who have no known forebears or sibs with mental illness, was obtained from the NIMH Schizophrenia Genetics Initiative. The 58 subjects in the initial screening were genetically unrelated.

A 27 amino acid segment (residues 264–290), identified as the tetrahydrobiopterin cofactor binding region of PAH [Jennings et al., 1991; Hufton et al., 1995] has 70% identity with residues 309–335 of TH and residues 251–277 of TPH (as published in GenBank). The genomic DNA corresponding to these amino acid residues in the PAH, TH and TPH genes were the minimal regions analyzed by automated DNA sequencing performed by Lark Technologies, Inc. (Houston, TX). In the course of this analysis, data for adjacent intron sequences were also obtained. The human genomic consensus sequences used were from GenBank or other published sources for PAH [Scriver et al., 2000], TH [O'Malley et al., 1987; Ishiguro et al., 1998], and TPH [Boularand et al., 1995; Nielsen et al., 1997].

For subjects identified with the PAH K274E mutation, genomic DNA from all available family members was obtained from the NIMH Schizophrenia Genetics Initiative for sequence analysis (by Lark Technologies, Inc.).

RESULTS

Based on the previous findings for the PAH K274E mutation [Richardson et al., 1999a,b], this study focused on the African-American subjects available from the NIMH Schizophrenia Genetics Initiative. One study group consisted of 41 subjects with psychiatric diagnoses of DSM-III-R schizophrenia, in which 31 of the subjects were female with a mean age of 50.5 years. The other study group consisted of 17 individuals assessed as never mentally ill, in which 15 of the subjects were female with a mean age of 67.1 years.

DNA analysis of the genomic sequences encoding the cofactor binding region of the PAH, TH and TPH genes, as well as adjacent intron sequences (IVS), resulted in the identification of several variants as presented in

TABLE I. Frequency of PAH, TH and TPH Variant Genotypes in Subjects With Schizophrenia and Never Mentally Ill Subjects

			Schizophrenia				Never mentally ill			
Gene	Sequence variation		n	Genotype: frequency			n	Genotype: frequency		
PAH	K274E	AAA/GAG	41	AA: 0.98	AG: 0.02	GG: 0	17	AA: 0.94	AG: 0.06	GG: 0
PAH	IVS7nt282	g/a	37	gg: 0.89	ga: 0.11	aa: 0	17	gg: 0.88	ga: 0.12	aa: 0
PAH	IVS7nt332	c/t	37	cc: 0.52	ct: 0.43	tt: 0.05	17	cc: 0.53	ct: 0.35	tt: 0.12
PAH	IVS7nt791	c/t	40	cc: 0.47	ct: 0.48	tt: 0.05	16	cc: 0.49	ct: 0.38	tt: 0.13
TH	IVS8nt8	c/t	39	cc: 0.64	ct: 0.36	tt: 0	17	cc: 0.76	ct: 0.24	tt: 0
TPH	IVS7nt13	a/g	38	aa: 0.73	ag: 0.24	gg: 0.03	17	aa: 0.65	ag: 0.35	gg: 0
TPH	IVS7nt779	c/a	37	cc: 0.65	ca: 0.32	aa: 0.03	17	cc: 0.71	ca: 0.29	aa: 0

Table I. The PAH K274E missense mutation in the cofactor binding domain was observed in one subject diagnosed with schizophrenia and one subject designated as never mentally ill. No other sequence variants were identified in the regions encoding the cofactor binding domains of the PAH, TH or TPH proteins. Single nucleotide polymorphisms in adjacent intron regions were observed in the PAH, TH and TPH genes. All of the genetic variants identified in the study were represented both in the schizophrenia group and in the never mentally ill group, with the frequencies as shown. Due to the observation of only one protein-coding mutation (PAH K274E) among the polymorphisms detected and the low frequency of that mutation, no statistical analyses were conducted.

The allele identified in Table I as TPH IVS7nt779 is equivalent to the site referred to as TPH intron 7 A779C in previous studies [Nielsen et al., 1994, 1998; New et al., 1998; Kunugi et al., 1999; Bennett et al., 2000; Nolan et al., 2000; Shinkai et al., 2000], except for C at that position in the consensus sequence referenced for the current analysis [Boularand et al., 1995]. The results from Table I indicate 779A frequencies of 0.189 in African-American schizophrenic subjects, 0.147 in African-American never mentally ill subjects and 0.176 in African-American subjects overall, which are appreciably lower than the 779A frequencies (ranging from 0.356–0.584) previously reported for other ethnic groups [Nielsen et al., 1997]. This TPH allele has been investigated for association with aggressive behavior [New et al., 1998; Nolan et al., 2000], negative symptoms [Shinkai et al., 2000], and suicidal behavior [Nielsen et al., 1994, 1998; Kunugi et al., 1999; Bennett et al., 2000], but in this cohort no evidence was found to support a relationship of TPH IVS7nt779 genotype with behavioral phenotype among the subjects with schizophrenia (data not shown).

For subjects with the PAH K274E mutation, DNA samples from all available family members were genotyped for sequence variants including the PAH K274E mutation and PAH L321L polymorphism (Fig. 1). The PAH L321L variant, a C to T substitution in the final nucleotide of codon 321, has previously been reported to occur in conjunction with PAH K274E [Richardson et al., 1999a,b; Acosta et al., 2001a]. In Family A, the PAH K274E mutation was identified in one of the three subjects with schizophrenia, and the PAH L321L variant was observed in the presence or absence of the K274E mutation. In Family B, the PAH K274E mutation was present in all available family members except for one schizophrenic subject. In all cases, the PAH K274E mutation was observed in the heterozygous state, and was accompanied by the PAH L321L polymorphism, either in the heterozygous or homozygous state.

DISCUSSION

The majority of genetic variants observed in this study population were intronic polymorphisms with no known functional consequences. The variant TPH IVS7nt779 is located in a polypyrimidine tract and although it has been reported that substitutions in such regions may affect splicing fidelity, no evidence for aberrant splicing has been found to be associated with substitution at this site [Nielsen et al., 1997]. Previous reports of associations between the TPH IVS7nt779 allele and clinical behavior were in patients of Caucasian, Hispanic or Asian ethnicity [Nielsen et al., 1994, 1998; New et al., 1998; Nolan et al., 2000; Shinkai et al., 2000] and there is currently no evidence for such relationships in African-American subjects.

The PAH K274E mutation, a lysine to glutamic acid substitution at amino acid 274 in the cofactor binding domain, was observed in this study in a total of seven subjects with mental disorders and one subject assessed as never mentally ill. A previous study identified the PAH K274E in four subjects with schizophrenia and (through analysis of family members) in one subject that was not mentally ill [Richardson et al., 1999a,b]. Other reports of the PAH K274E mutation provided no psychiatric information for the study subjects [Acosta et al., 2001a,b]. In all known cases, the PAH K274E mutation is accompanied by the PAH L321L variant. There is no predicted change in the protein sequence for the PAH L321L variant, which resides in the catalytic domain of the enzyme, but there is evidence for a higher frequency for this variant in African-Americans compared to other ethnic groups [Richardson et al., 1999a,b; Acosta et al., 2001a].

The high frequency for the PAH K274E mutation in Family B (Fig. 1), coincides with a preponderance of mental illness among the family members. Large-scale genetic analyses for the PAH K274E mutation (especially in those of African-American ethnicity) in families and/or in a case-control study with sufficient statistical

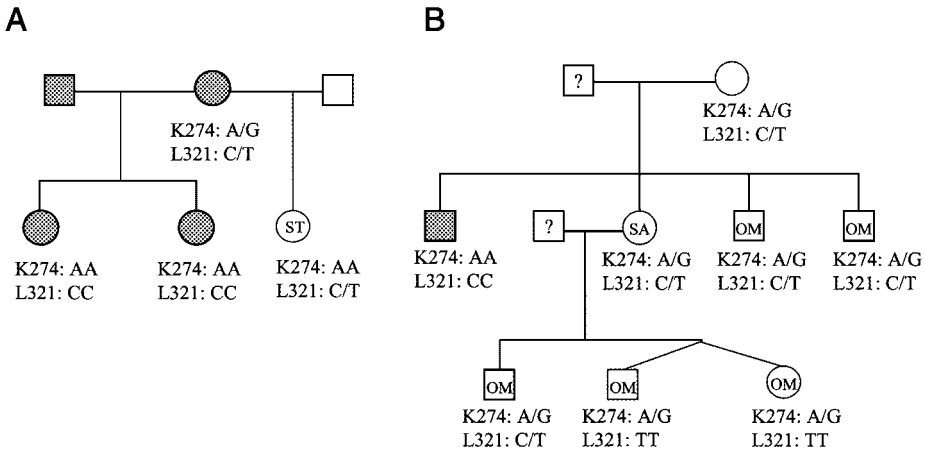

Fig. 1. Pedigree drawings for two families from the NIMH Schizophrenia Genetics Initiative including psychiatric phenotype, and genotypes for PAH K274 and PAH L321, in all subjects with DNA available. The psychiatric phenotype is depicted as follows: filled symbol, DSM-III-R schizophrenia; open symbol, never mentally ill; SA, DSM-III-R schizoaffective disorder-depressive type; ST, DSM-III-R schizotypal personality disorder, etc.; OM, other mental disorder; ?, unknown.

power to accommodate the low frequency of the K274E mutation, would be necessary to determine whether there is an association between PAH genotype and psychiatric phenotype.

In this study no sequence variants were observed in the cofactor binding regions of the TH or TPH gene. This may be due to ethnic differences in mutation frequency because previous findings of TH and TPH mutations have been in Caucasian or Asian cohorts [Ludecke et al., 1996; Ishiguro et al., 1998; Kunugi et al., 1998; Van den Heuvel et al., 1998; Paoloni-Giacobino et al., 2000]. Further analysis of the functionally critical cofactor binding region of TH and TPH in ethnically diverse cohorts, in a case-control design with correction for population stratification or in a family study using the transmission disequilibrium test, may reveal additional mutations in these amino acid hydroxylases that could affect neurotransmitter synthesis and the pathophysiology of schizophrenia.

ACKNOWLEDGMENTS

The authors wish to thank Dr. L. Li and R. Sugarek of Lark Technologies, Inc. and M. Bevans for technical support. Data and biomaterials were collected in three projects that participated in the National Institute of Mental Health (NIMH) Schizophrenia Genetics Initiative. From 1991–97, the Principal Investigators and Co-Investigators were: Harvard Univ., Boston, MA, MH46318, Drs. M.T. Tsuang, S. Faraone, and J. Pepple; Washington Univ., St. Louis, MO, MH46276, Drs. C.R. Cloninger, T. Reich, and D. Svrakic; Columbia Univ., New York, NY, MH46289, Drs. C. Kaufmann, D. Malaspina, and J.H. Friedman. Funding for this research was provided by NIMH grant MH62352-01 to Dr. H. M. Chao.

REFERENCES

Acosta AX, Silva WA, Carvalho TM, Gomes M, Zago MA. 2001a. Mutations of the phenylalanine hydroxylase (PAH) gene in Brazilian patients with phenylketonuria. Hum Mutat 17:122–130.

Acosta AX, Silva WA Jr, Carvalho TM, Zago MA. 2001b. Ten novel mutations in the phenylalanine hydroxylase gene (PAH) observed in Brazilian patients with phenylketonuria. Hum Mutat 17:77.

Bellivier F, Leboyer M, Courtet P, Buresi C, Beaufils B, Samolyk D, Allilaire JF, Feingold J, Mallet J, Malafosse A. 1998. Association between the tryptophan hydroxylase gene and manic-depressive illness. Arch Gen Psychiatry 55:33–37.

Bennett PJ, McMahon WM, Watabe J, Achilles J, Bacon M, Coon H, Grey T, Keller T, Tate D, Tcaciuc I, Workman J, Gray D. 2000. Tryptophan hydroxylase polymorphisms in suicide victims. Psychiatr Genet 10: 13–17.

Boularand S, Darmon MC, Mallet J. 1995. The human tryptophan hydroxylase gene. An unusual splicing complexity in the 5′-untranslated region. J Biol Chem 270:3748–3756.

Cloninger CR, Kaufmann CA, Faraone SV, Malaspina D, Svrakic DM, Harkavy-Friedman J, Suarez BK, Matise TC, Shore D, Lee H, Hampe CL, Wynne D, Drain C, Markel PD, Zambuto CT, Schmitt K, Tsuang MT. 1998. Genome-wide search for schizophrenia susceptibility loci: the NIMH Genetics Initiative and Millennium Consortium. Am J Med Genet 81:275–281.

Frisch A, Postilnick D, Rockah R, Michaelovsky E, Postilnick S, Birman E, Laor N, Rauchverger B, Kreinin A, Poyurovsky M, Schneidman M, Modai I, Weizman R. 1999. Association of unipolar major depressive disorder with genes of the serotonergic and dopaminergic pathways. Mol Psychiatry 4:389–392.

Furlong RA, Ho L, Rubinsztein JS, Walsh C, Paykel ES, Rubinsztein DC. 1998. No association of the tryptophan hydroxylase gene with bipolar affective disorder, unipolar affective disorder, or suicidal behavior in major affective disorder. Am J Med Genet 81:245–247.

Hufton SE, Jennings IG, Cotton RG. 1995. Structure and function of the aromatic amino acid hydroxylases. Biochem J 311:353–366.

Ishiguro H, Arinami T, Saito T, Akazawa S, Enomoto M, Mitushio H, Fujishiro H, Tada K, Akimoto Y, Mifune H, Shiozuka S, Hamaguchi H, Toru M, Shibuya H. 1998. Systematic search for variations in the tyrosine hydroxylase gene and their associations with schizophrenia, affective disorders, and alcoholism. Am J Med Genet 81:388–396.

Jennings IG, Kemp BE, Cotton RG. 1991. Localization of cofactor binding sites with monoclonal anti-idiotype antibodies: phenylalanine hydroxylase. Proc Natl Acad Sci USA 88:5734–5738.

Jonsson EG, Geijer T, Gyllander A, Terenius L, Sedvall GC. 1998. Failure to replicate an association between a rare allele of a tyrosine hydroxylase gene microsatellite and schizophrenia. Eur Arch Psychiatry Clin Neurosci 248:61–63.

Joyce JN. 1993. The dopamine hypothesis of schizophrenia: limbic interactions with serotonin and norepinephrine. Psychopharmacology 112: S16–S34.

Kirov G, Owen MJ, Jones I, McCandless F, Craddock N. 1999. Tryptophan hydroxylase gene and manic-depressive illness. Arch Gen Psychiatry 56:98–99.

Kunugi H, Kawada Y, Hattori M, Ueki A, Otsuka M, Nanko S. 1998. Association study of structural mutations of the tyrosine hydroxylase gene with schizophrenia and Parkinson disease. Am J Med Genet 81: 131–133.

Kunugi H, Ishida S, Kato T, Sakai T, Tatsumi M, Hirose T, Nanko S. 1999. No evidence for an association of polymorphisms of the tryptophan hydroxylase gene with affective disorders or attempted suicide among Japanese patients. Am J Psychiatry 156:774–776.

Ledley FD, Grenett HE, Bartos DP, Van Tuinen P, Ledbetter DH, Woo SL. 1987. Assignment of human tryptophan hydroxylase locus to chromosome 11: gene duplication and translocation in evolution of aromatic amino acid hydroxylases. Somat Cell Mol Genet 13:575–580.

Lieberman JA, Mailman RB, Duncan G, Sikich L, Chakos M, Nichols DE, Kraus JE. 1998. Serotonergic basis of antipsychotic drug effects in schizophrenia. Biol Psychiatry 44:1099–1117.

Ludecke B, Knappskog PM, Clayton PT, Surtees RA, Clelland JD, Heales SJ, Brand MP, Bartholome K, Flatmark T. 1996. Recessively inherited L-DOPA-responsive parkinsonism in infancy caused by a point mutation (L205P) in the tyrosine hydroxylase gene. Hum Mol Genet 5:1023–1028.

McQuillin A, Lawrence J, Kalsi G, Chen A, Gurling H, Curtis D. 1999. No allelic association between bipolar affective disorder and the tryptophan hydroxylase gene. Arch Gen Psychiatry 56:99–101.

Meloni R, Laurent C, Campion D, Ben Hadjali B, Thibaut F, Dollfus S, Petit M, Samolyk D, Martinez M, Poirier MF, Mallet J. 1995. A rare allele of a microsatellite located in the tyrosine hydroxylase gene found in schizophrenic patients. Comptes Rendus De L Academie Des Sciences-Serie Iii, Sciences De La Vie 318:803–809.

New AS, Gelernter J, Yovell Y, Trestman RL, Nielsen DA, Silverman J, Mitropoulou V, Siever LJ. 1998. Tryptophan hydroxylase genotype is associated with impulsive-aggression measures: a preliminary study. Am J Med Genet 81:13–17.

Nielsen DA, Goldman D, Virkkunen M, Tokola R, Rawlings R, Linnoila M. 1994. Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism. Arch Gen Psychiatry 51:34–38.

Nielsen DA, Jenkins GL, Stefanisko KM, Jefferson KK, Goldman D. 1997. Sequence, splice site and population frequency distribution analyses of the polymorphic human tryptophan hydroxylase intron 7. Brain Res Mol Brain Res 45:145–148.

Nielsen DA, Virkkunen M, Lappalainen J, Eggert M, Brown GL, Long JC, Goldman D, Linnoila M. 1998. A tryptophan hydroxylase gene marker for suicidality and alcoholism. Arch Gen Psychiatry 55:593–602.

Nolan KA, Volavka J, Lachman HM, Saito T. 2000. An association between a polymorphism of the tryptophan hydroxylase gene and aggression in schizophrenia and schizoaffective disorder. Psychiatr Genet 10: 109–115.

O'Malley KL, Anhalt MJ, Martin BM, Kelsoe JR, Winfield SL, Ginns EI. 1987. Isolation and characterization of the human tyrosine hydroxylase gene: identification of 5′ alternative splice sites responsible for multiple mRNAs. Biochemistry 26:6910–6914.

Paoloni-Giacobino A, Mouthon D, Lambercy C, Vessaz M, Coutant-Zimmerli S, Rudolph W, Malafosse A, Buresi C. 2000. Identification and analysis of new sequence variants in the human tryptophan hydroxylase (TpH) gene. Mol Psychiatry 5:49–55.

Pardridge WM, Choi TB. 1986. Neutral amino acid transport at the human blood-brain barrier. Fed Proc 45:2073–2078.

Richardson MA, Guttler F, Guldberg P, Read L, Clelland J, Chao H, Reilly M, Suckow R. 1999a. Functional and psychiatric associations of the phenylalanine hydroxylase gene. Mol Psychiatry 4:S41.

Richardson MA, Guttler F, Guldberg P, Reilly M, Suckow R, Read L, Chao H, Clelland J. 1999b. Phenylalanine hydroxylase gene mutation associated with schizophrenia and African-American ethnic status. Schizophr Res 36:95.

Scriver CR, Waters PJ, Sarkissian C, Ryan S, Prevost L, Cote D, Novak J, Teebi S, Nowacki PM. 2000. PAHdb: a locus-specific knowledge base. Hum Mutat 15:99–104.

Shinkai T, Ohmori O, Suzuki T, Kojima H, Hori H, Terao T, Nakamura J. 2000. Polymorphisms of tryptophan hydroxylase gene and the symptomatology of schizophrenia: an association study. Psychiatr Genet 10: 165–171.

Van den Heuvel LP, Luiten B, Smeitink JA, de Rijk-van Andel JF, Hyland K, Steenbergen-Spanjers GC, Janssen RJ, Wevers RA. 1998. A common point mutation in the tyrosine hydroxylase gene in autosomal recessive L-dopa-responsive dystonia in the Dutch population. Hum Genet 102: 644–646.

Van Kammen DP, Kelley M. 1991. Dopamine and norepinephrine activity in schizophrenia. An integrative perspective. Schizophr Res 4:173–191.

Waters PJ, Parniak MA, Nowacki P, Scriver CR. 1998. In vitro expression analysis of mutations in phenylalanine hydroxylase: linking genotype to phenotype and structure to function. Hum Mutat 11:4–17.

Wei J, Ramchand CN, Hemmings GP. 1995. Association of polymorphic VNTR region in the first intron of the human TH gene with disturbances of the catecholamine pathway in schizophrenia. Psychiatr Genet 5: 83–88.