ELSEVIER

European Journal of Pharmacology 410 (2000) 165–181

ejp

www.elsevier.nl/locate/ejphar

Pharmacogenetics and the serotonin system: initial studies and future directions

Jeremy Veenstra-VanderWeele [a], George M. Anderson [b], Edwin H. Cook Jr. [a,c,*]

[a] *Laboratory of Developmental Neuroscience, Child and Adolescent Psychiatry, Department of Psychiatry, University of Chicago, MC3077, 5841 S. Maryland Avenue, Chicago, IL 60637, USA*

[b] *Departments of Laboratory Medicine and Child Psychiatry, Yale University School of Medicine, New Haven, CT, USA*

[c] *Department of Pediatrics and Committee on Clinical Pharmacology, University of Chicago, MC3077, 5841 S. Maryland Avenue, Chicago, IL 60637, USA*

Accepted 20 October 2000

Abstract

Serotonin (5-hydroxytryptamine, 5-HT) appears to play a role in the pathophysiology of a range of neuropsychiatric disorders, and serotonergic agents are of central importance in neuropharmacology. Genes encoding various components of the 5-HT system are being studied as risk factors in depression, schizophrenia, obsessive–compulsive disorder, aggression, alcoholism, and autism. Recently, pharmacogenetic research has begun to examine possible genetic influences on therapeutic response to drugs affecting the serotonin system. Genes regulating the synthesis (*TPH*), storage (*VMAT2*), membrane uptake (*HTT*), and metabolism (*MAOA*) of 5-HT, as well as a number of 5-HT receptors (*HTR1A*, *HTR1B*, *HTR2A*, *HTR2C*, and *HTR5A*), have been studied and this initial research is reviewed here. After a brief introduction to serotonin neurobiology and a general discussion of appropriate genetic methodology, each of the major 5-HT-related genes and their encoded proteins are reviewed in turn. For each gene, relevant polymorphisms and research on functional variants are discussed; following brief reviews of the disorder or trait association and linkage studies, pharmacogenetic studies performed to date are covered. The critical and manifold roles of the serotonin system, the great abundance of targets within the system, the wide range of serotonergic agents—available and in development—and the promising preliminary results suggest that the serotonin system offers a particularly rich area for pharmacogenetic research.

Keywords: Pharmacogenetics; 5-HT (5-hydroxytryptamine, serotonin); Tryptophan hydroxylase; 5-HT receptor; 5-HT (5-hydroxytryptamine, serotonin) transporter; Monoamine oxidase; 5-HT (5-hydroxytryptamine, serotonin) reuptake inhibitor, selective; Clozapine

1. Introduction

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been implicated in a wide range of psychiatric conditions including depression, anxiety disorders, obsessive–compulsive disorder, psychosis, eating disorders, and substance abuse and dependence (for a review, see Lucki (1998), or for a series of reviews, see a dedicated issue of the Annals of New York Academy of Sciences (vol. 600, 1990)). Many of the drugs currently used most frequently in psychiatry, such as the 5-HT reuptake inhibitors, the atypical antipsychotics, the monoamine oxidase inhibitors, and the anxiolytic drug buspirone, have serotonin neurons as their principal site of action. Hallucinogenic drugs like lysergic acid diethylamide (LSD) and psylocibin, as well as the euphoriant (+)-3,4-methylenedioxyamphetamine (MDMA, "ecstasy"), also act via the serotonin system. Other drugs like the anxiolytic benzodiazepines may indirectly affect serotonin dynamics (Sibille et al., 2000). Interest in 5-HT has also been stimulated by several long-standing and well-replicated observations of altered 5-HT neurochemistry. Findings include elevated whole blood 5-HT in autism (for a review, see Cook and Leventhal (1996)) and low cerebrospinal fluid levels of the 5-HT metabolite 5-hydroxyindoleacetic acid in violent suicide or impulsive aggression (for a review, see Linnoila and Virkkunen (1992)).

* Corresponding author. Laboratory of Developmental Neuroscience, Child and Adolescent Psychiatry, Department of Psychiatry, University of Chicago, MC3077, 5841 S. Maryland Avenue, Chicago, IL 60637, USA. Tel.: +1-773-702-9692; fax: +1-773-702-9929; http://psy-svr1.uchicago.edu/ldn.

E-mail address: ed@yoda.bsd.uchicago.edu (E.H. Cook Jr.).

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00814-1

The 5-HT molecule also has a role outside of its traditional place in neuropsychiatry. Peripherally, 5-HT is produced in enterchromaffin cells of the intestine. Free 5-HT is taken up and stored by platelets; subsequent release during platelet activation contributes to hemostatic processes. Serotonin is capable of both vasoconstrictive and vasodilatory effects via vascular 5-HT receptors (for a review, see Frishman and Grewall (2000)). Vascular 5-HT receptors in cerebral arteries and elsewhere appear to mediate the anti-migraine treatment effects of 5-$HT_{1B/D}$ receptor agonists such as sumatriptan (Peroutka and McCarthy, 1989). Furthermore, activation of atrial 5-HT_4 receptors appears to be important in cardiac arrhythmias (Laer et al., 1998; Pino et al., 1998). The serotonin system is also important in the regulation of gut motility and has been suggested to be involved in irritable bowel syndrome (Sanger, 1996). Prokinetic benzamides such as cisapride have antagonistic activity at both the 5-HT_3 and 5-HT_4 gut receptors (Nagakura et al., 1999). Finally, selective 5-HT_3 receptor antagonists like ondansetron are currently the most effective antiemetic medications (Chaffee and Tankanow, 1991).

Clearly 5-HT physiology is complex: centrally and peripherally 5-HT appears to act as a neurotransmitter and neuromodulator, with additional peripheral neurocrine and other endocrine-like roles. Within the brain, the raphe nuclei contain the cell bodies of 5-HT neurons projecting to various regions throughout the brain. A number of important 5-HT-related proteins are found in these neurons, and in other 5-HT-containing cells. The enzyme tryptophan hydroxylase catalyzes the rate-limiting step in the conversion of tryptophan to 5-HT. The vesicular monoamine transporter type-2 (VMAT2) transports 5-HT into presynaptic vesicles. Once released extracellularly, 5-HT binds to postsynaptic receptor proteins, thereby transmitting a signal from one cell to the next. However, 5-HT also binds to presynaptic 5-HT_{1A} and 5-$HT_{1B/D}$ autoreceptors that modulate the further release of 5-HT. The family of 5-HT receptors is summarized in Table 1. The serotonin transporter protein facilitates reuptake of 5-HT out of the synapse, and has a predominant role in the termination of the extracellular effects of 5-HT. Monoamine oxidase-A catalyzes the breakdown of 5-HT and plays an important part in the regulation of intracellular 5-HT levels. A model serotonin synapse depicting the proteins of interest as well as their interactions with some of the medications in common use is presented in Fig. 1.

The application of pharmacogenetics to the 5-HT system holds much promise, both for clinical decision-making and for achieving a better understanding of the serotonin system itself. Until recently, the only pharmacogenetics research of relevance to the serotonin system involved studies of metabolic enzyme variants affecting the pharmacokinetics of various antidepressants (for a review, see Bertilsson et al. (1997)). The availability of gene sequence data (both cDNA and genomic DNA sequence), and the discovery of a number of apparent functional variants of 5-HT-related genes, including the serotonin transporter (Fiskerstrand et al., 1999; Heils et al., 1996; Lesch et al.,

Table 1
5-HT receptors

Receptor	Signaling	Notes	Chromosome	LocusID	Pharmacotherapy
5-HT_{1A}	−AC	Knockout anxious, benzodiazepine-resistant	5q11.2-13	3350	Buspirone, pindolol
5-HT_{1B}	−AC	= 5-$HT_{1D\beta}$; Knockout aggressive, consumes more EtOH, cocaine; Arterial dilation	6q13	3351	Sumatriptan
5-HT_{1D}	−AC	= 5-$HT_{1D\alpha}$; Pseudogene disrupted by Alu sequence; Arterial dilation	1p34.3-36.3	3352	Sumatriptan
5-HT_{1E}	−AC	= S31	6q14-15	3354	
5-HT_{1F}	−AC	= 5-HT_{1E} = MR77	3p12	3355	
5-HT_{2A}	PLC	= 5-HT_2	13q14.1-14.2	3356	Clozapine, LSD
5-HT_{2B}	PLC	= 5-HT_{2F}	2q36.3-37.1	3357	
5-HT_{2C}	PLC, GC	= 5-HT_{1C}; Knockout obese, spontaneous fatal seizures	Xq24	3358	Clozapine, LSD
5-HT_{3A}	Na^+/Ca^{2+} channel	Splice variants; gut motility	11q23.1-23.2	3359	Ondansetron
5-HT_{3B}	Na^+/Ca^{2+} channel	Forms heteromer with 5-HT_{3A}	11q23.1-23.2	9177	Ondansetron
5-HT_4	+AC	2 splice variants: 5-HT_{4L}, 5-HT_{4S}; Atrial arrhythmias, gut motility	5q33.2	3360	Zacopride
5-HT_{5A}		= REC17; Knockout explores more, LSD-insensitive	7q34-36	3361	LSD
5-HT_6	+AC	= St-B17	1p35-36	3362	LSD
5-HT_7	+AC	80–90% homologous pseudogene; gut motility	10q23.3-24.3	3363	Clozapine, LSD

AC—Adenylyl cyclase; PLC—Phospholipase C; GC—Guanylyl Cylase.
Locus Link web page available at http://www.ncbi.nlm.nih.gov/LocusLink/.

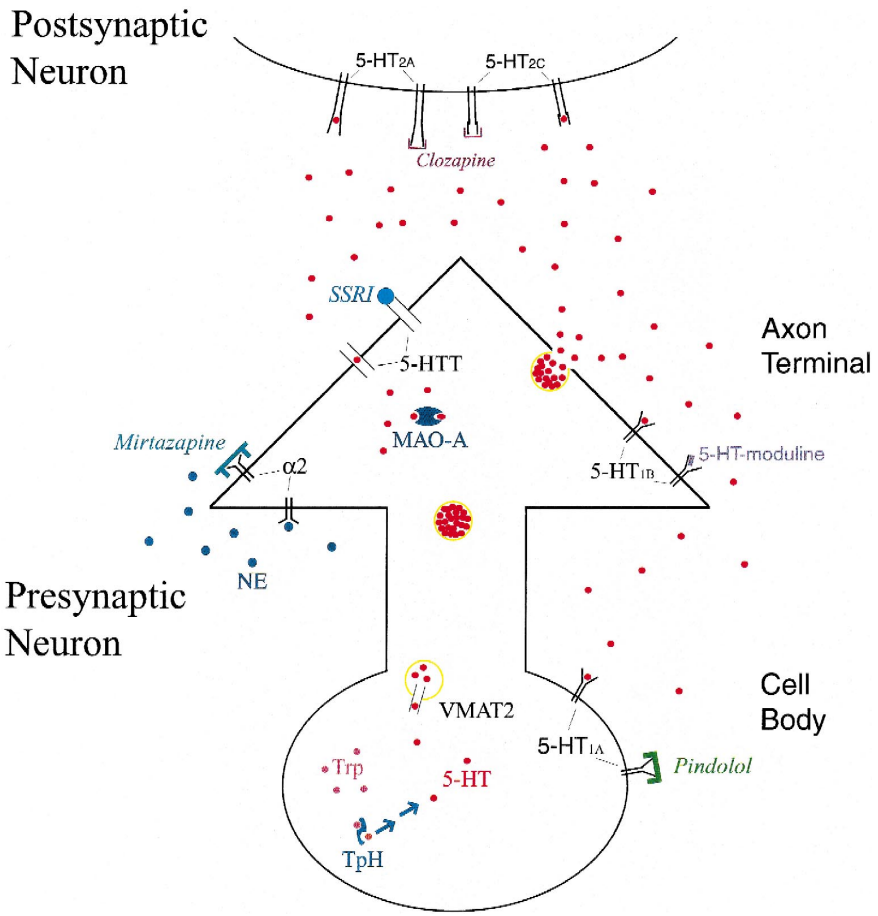

Fig. 1. Model serotonin synapse. Simplified serotonin synapse, including many of the components currently under pharmacogenetic investigation. Serotonin (5-hydroxytryptamine or 5-HT) is shown from synthesis to synaptic release and then binding to presynaptic and postsynaptic receptors. Tryptophan hydroxylase (TpH) catalyzes the rate-limiting step in the synthesis of 5-HT from tryptophan (Trp). The vesicular monoamine transporter type-2 (VMAT2) transports 5-HT into presynaptic vesicles. These vesicles then release 5-HT extraneuronally, where 5-HT interacts with postsynaptic receptors including 5-HT_{2A} and 5-HT_{2C}. 5-HT also binds to somatodendritic (5-HT_{1A}) and terminal (5-HT_{1B}) autoreceptors. An endogenous tetrapeptide 5-HT-moduline (Leu–Ser–Ala–Leu) has been found to specifically interact with 5-$HT_{1B/1D}$ receptors and desensitize autoreceptor response to 5-HT (Chennaoui et al., 2000; Grimaldi et al., 1999). The serotonin transporter (5-HTT) transports 5-HT from the extraneuronal space back into the presynaptic neuron. Within the presynaptic neuron, monoamine oxidase-A (MAO-A) breaks down 5-HT. Norepinephrine (NE) impacts upon the serotonin neuron by binding to α_2-adrenergic heteroreceptors at the terminal. A number of drugs in common usage interact with components of the serotonin system. Clozapine is shown antagonizing 5-HT activity at the 5-HT_{2A} and 5-HT_{2C} receptors. A selective serotonin reuptake inhibitor (SSRI) is shown blocking the 5-HTT. Monoamine oxidase inhibitors (not shown) antagonize monoamine oxidase-A. Pindolol is shown antagonizing 5-HT activity at the 5-HT_{1A} autoreceptor. The antagonist mirtazapine is depicted interacting with the $\alpha 2$ heteroreceptor.

1996; MacKenzie and Quinn, 1999), the 5-HT 1A, 2A, and 2C receptors (Ozaki et al., 1997; Rotondo et al., 1997), and monoamine oxidase-A (Deckert et al., 1999; Sabol et al., 1998), has changed the picture dramatically.

After a general discussion of appropriate genetic methodology, we will review, in turn, each of the major 5-HT-related genes and their encoded proteins. For each gene, we will first discuss the relevant polymorphisms that have been identified, focusing on variants with a possible functional role. Following a brief review of the association and linkage studies that have been carried out in various neuropsychiatric disorders, we will discuss the pharmacogenetic studies that have been performed to date. The overview of the molecular and pharmacogenetic research on the serotonin transporter gene will be especially extensive given the importance of the encoded protein, the wide use of agents acting at the transporter, and the large number of association and pharmacogenetic studies performed. Due to the limitations of space, we will review only those 5-HT receptors for which either pharmacogenetic data are available or genetic variants have been identified. Thus, we will be forced to neglect receptors such as the 5-HT_7, where preliminary studies are just emerging (Lassig et al., 1999). It should be noted that eventually most of the receptors, along with their modulators and components of their signaling cascades, will be of interest. A recent, more general, review of neuropsychiatric pharmacogenetics covers some of the ground sur-

veyed here (Anderson and Cook, 2000); however, much of the work with 5-HT-related genes has occurred in the past year.

2. Methodology of pharmacogenetic studies

Before discussing the various studies exploring genetic influences within the serotonin system, it is important to address the methodology with which gene association studies should be conducted. The first studies of genetic effects on pharmacological response have compared drug response in subjects grouped according to genotype. This approach is liable to the same errors that have been noted in case-controlled association studies with disease. As non-replicated case-controlled disorder association studies accumulated, genetic epidemiologists identified biases that could contribute to false positive findings. The most prominent of these was population stratification, in which the cases and controls are drawn from different subpopulations with discrepant gene frequencies (Kang et al., 1999; Spielman et al., 1993). The risk of admixture artifact was also noted in populations that have undergone non-random mating for only a few generations (Ewens and Spielman, 1995; Spielman and Ewens, 1996). Some investigators have sought to identify homogeneous populations that will eliminate these biases. However, studies focusing on one ethnic group or subgroup may not generalize to the larger population.

In response to the biases inherent in case-controlled studies, family-based studies utilizing the transmission/disequilibrium test (TDT) have come to represent the gold standard in detection of linkage in the presence of association. These studies eliminate the impact of population stratification (Spielman et al., 1993; Thomson, 1995) and admixture artifact (Ewens and Spielman, 1995; Spielman and Ewens, 1996). Additionally, Allison (1997) and others have described the use of TDT for quantitative traits (Allison, 1997; Waldman et al., 1999). This methodology allows pharmacogenetic studies to focus on gradations of response to a drug, rather than using categorical response and nonresponse groupings. Unfortunately for those trying to apply family-based methods, it can be difficult or impossible to collect DNA from parents of older psychiatric patients. An alternative TDT approach to the standard parent–child trio uses samples of sibling pairs to test for association (Spielman and Ewens, 1998). This method may be applied when parents are unavailable or when sibling pair DNA has already been collected.

Given the difficulty and cost of acquiring DNA from parents, investigators have begun looking for ways of controlling for non-independence within a case-controlled sample. One of the methods suggested is "Genomic Control" (GC), which uses 20–60 single nucleotide polymorphisms spread throughout the genome to estimate the degree of population stratification. The significance level of a candidate gene single nucleotide polymorphism is then adjusted to reflect true association in the face of population substructure (Bacanu et al., 2000). Pritchard et al. (2000) have suggested an alternative method that assigns subjects to putative genetic subpopulations based on genotypes at 100 unlinked microsatellite markers throughout the genome. Testing for association within these genetic subpopulations will in theory eliminate the hazards of unknown population substructure. While simulations have suggested that these methods should prove useful, they have yet to be applied to real data.

Since case-controlled disorder association studies are likely to yield false positive results, we will focus here only on those disorder association studies that used a family-based methodology. However, in the pharmacogenetic literature, few of the initial studies of the serotonin system have utilized either family-based or population-based methods to control for population stratification and other biases. Although we will review this literature, the data stemming from these studies, while often exciting, must be seen as preliminary and requiring replication using more rigorous methodology.

3. Research on serotonin-related genes

3.1. Tryptophan hydroxylase

The human tryptophan hydroxylase gene (*TPH*) is located on chromosome 11p14-15.3 and encodes the enzyme that catalyzes the rate-limiting step in the synthesis of 5-HT from tryptophan. For this reason, *TPH* variants might be involved in any of the phenotypes thought to involve dysfunction of the 5-HT system. Various *TPH* polymorphisms have been detected, but none have been shown to be functional (Nielsen et al., 1997). Nielsen et al. (1997) used sib-pair analysis to assess the relationship between an intron 7 polymorphism, 779-A/C, and suicidality and alcoholism in a Finnish sample. They found significant linkage between this polymorphism and both severe suicide attempts and non-antisocial alcoholism. This study awaits family-based replication, but it is supported by case-controlled data suggesting associations between several *TPH* polymorphisms and both suicidality and antisocial alcoholism (Ishiguro et al., 1999b; Mann et al., 1997; Nielsen et al., 1994; Rotondo et al., 1999; Tsai et al., 1999). Identification of functional *TPH* variants affecting gene expression or enzyme activity would be of interest given the number of positive studies and the central role played by tryptophan hydroxylase in the production of 5-HT.

3.2. Vesicular monoamine transporter type-2

The vesicular monoamine transporter type-2 (VMAT2) loads 5-HT and a number of other monoamines into presynaptic vesicles. Like tryptophan hydroxylase, it helps

regulate the supply of 5-HT available for release. Experiments using VMAT2 gene knockout mice have primarily examined the role of the VMAT2 within the dopamine system, revealing a heightened sensitivity to dopamine agonists, cocaine, and amphetamines in mice lacking the vesicular transporter (Takahashi et al., 1997; Wang et al., 1997). One study focusing on the serotonin system found decreased quantal release of 5-HT from mast cells of VMAT2 gene knockout heterozygote mice (Travis et al., 2000). Shih et al. (1999) found that tetrabenazine, a selective VMAT2 inhibitor, and ketanserin, a VMAT2 inhibitor and antagonist at 5-HT_{2A} and 5-HT_{2C} receptors, abolished aggressive behavior in the monoamine oxidase-A gene knockout animals. Persico et al. (1995) excluded close linkage between schizophrenia and a restriction fragment length polymorphism at the VMAT2 gene locus. While no functional polymorphisms have been identified in the VMAT2 gene (*SLC18A2*), located on chromosome 10q25, the gene bears study in a number of phenotypes, including aggression and drug abuse.

3.3. 5-HT_{2A} receptor

The 5-HT_{2A} receptor is a post-synaptic G protein-linked receptor that activates phosphoinositide hydrolysis. Interest in this receptor has been stimulated by its possible roles in hallucinations and psychosis. Two key observations have sparked this interest. First, agonists at the 5-HT_{2A} receptor, including lysergic acid diethylamide (LSD), have hallucinogenic properties that correspond to their affinities for these receptors (Aghajanian and Marek, 1999; Glennon et al., 1984). Second, clozapine and other atypical antipsychotic agents act as antagonists at 5-HT_{2A} receptors, and this appears to be an important component of their therapeutic action (Meltzer et al., 1989). Thus, it is not surprising that the role of the 5-HT_{2A} receptor gene (*HTR2A*) in the pathogenesis and treatment of schizophrenia has been extensively studied.

A number of polymorphisms, including several amino acid variants (also termed missense or non-synonymous polymorphisms, such variants alter protein amino acid sequence), have been identified within *HTR2A* on chromosome 13q14.1-14.2. The most common of the amino acid variants is His452Tyr in the C-terminal region of the receptor, with the 452Tyr allele showing a 9% frequency in Caucasian subjects (Ozaki et al., 1997). Ozaki et al. (1997) examined the effect of His452Tyr genotype on platelet 5-HT_{2A} receptor function in subjects with seasonal affective disorder. They found no genotype-dependent differences in platelet 5-HT_{2A} binding, but they did find that 5-HT-induced calcium response was significantly blunted in the heterozygous (452-His/Tyr) subjects. Follow-up studies are warranted, using both in vitro receptor expression models and family-based association designs.

The other frequent *HTR2A* polymorphisms appear unlikely to affect function of the 5-HT_{2A} receptor. Spurlock et al. (1998) analyzed a −1438 G/A single nucleotide polymorphism in the promoter region and found no effect of genotype on basal or cAMP- and protein kinase C-induced gene transcription in HeLa cells. Further, they found no difference in lymphocyte *HTR2A* mRNA expression between −1438 G/G and A/A homozygotes. On the other hand, in a small postmortem study, Turecki et al. (1999a) report higher prefrontal 5-HT_{2A} binding in subjects with the −1438-A allele. Additional analysis of the functional effects of the −1438 G/A polymorphism is needed to resolve this discrepancy. A few rare polymorphisms have also been described, including two rare amino acid variants with frequencies under 1%, Ala477Val and Thr25Asn (Erdmann et al., 1996; Ozaki et al., 1996).

While much attention has focused on *HTR2A* polymorphisms, few family-based association studies have been performed. One family-based study reported significant association in the presence of linkage between schizophrenia and the C allele at a 102-T/C polymorphism in a group of United Kingdom families, most of which were multiplex (Spurlock et al., 1998). This finding is not consistent with a negative TDT in a group of Irish subjects from multiplex families (Hawi et al., 1997). These contradictory results may reflect genetic heterogeneity, or alternatively, they may reflect different patterns of linkage disequilibrium across populations. Given that the 102 T/C polymorphism is unlikely to be functional, and the −1438 G/A polymorphism in nearly perfect linkage disequilibrium with it has not been demonstrated to be functional (Nakamura et al., 1999; Spurlock et al., 1998), linkage may be due to a nearby functional variant. Family-based association studies using additional markers, perhaps including haplotype analysis, may help resolve these findings.

Genetic studies of alcoholism and drug abuse are usually considered disorder association studies (see Uhl (1999) for a thorough review of this area). However, the genetic contribution to substance dependence may reflect specific pharmacogenetic influences on drug response or a more general genetic predisposition to substance abuse or drug-seeking behavior, or both. Since no family-based *HTR2A* association studies have been performed in this area, we will briefly consider the exploratory case-controlled studies. Nakamura et al. (1999) found a significant association between alcoholism in a subset of patients with aldehyde dehydrogenase mutations and the −1438 G allele (previously shown to be in tight linkage disequilibrium with the 102 C allele). Schuckit et al. (1999), on the other hand, found no association between low level of response to alcohol or alcohol dependence and either the 102 T/C single nucleotide polymorphism or the His452Tyr variant. Carefully controlled studies of *HTR2A* are needed to clarify these findings.

The initial pharmacogenetic studies examining the influence of the 5-HT_{2A} receptor on response to psychopharmacological agents have focused on clozapine. Clozapine

is often used in treating schizophrenic patients intolerant or unresponsive to other treatments. In such patients, clozapine has a response rate of approximately 50% (Lieberman et al., 1994). If genetic testing could predict which patients are least likely to benefit from clozapine treatment, significant cost and risk could be avoided. The initial studies on clozapine response have all followed the case-controlled format, and it is not surprising that disparate results have been obtained in different populations. While no studies have systematically addressed *HTR2A* allele frequencies across a range of ethnic groups, the −1438 G/A and 102 T/C single nucleotide polymorphisms have been reported to have differing frequencies in the Japanese and European populations (Nakamura et al., 1999). Arranz et al. (1998) performed a meta-analysis of the various studies reporting both positive and negative association between clozapine response and the 102 T/C and His452Tyr polymorphisms. They found significant association between the 102 C allele and clozapine response within the meta-analyzed sample of eight studies, but this significance disappeared when the original study (Arranz et al., 1995) was excluded. They report stronger association in studies with larger sample sizes and longer durations of treatment, but they did not perform a statistical analysis of this relationship. Their meta-analysis of the four studies examining the His452Tyr polymorphism revealed significant association with the 452Tyr allele. A subsequent large case-controlled association study in an ethnically diverse United States sample revealed significant association between clozapine response over 6 months and the 452Tyr allele, but not the 102 C allele (Masellis et al., 1998). Haplotype analyses when available did not show stronger association with clozapine response (Arranz et al., 1998; Masellis et al., 1998).

Even if the association between clozapine response and the two *HTR2A* polymorphisms is replicated using family-based methods, they appear to make only a modest contribution to determining clozapine response. Using the most generous estimate based on the meta-analysis data excluding the study of shortest duration, the positive predictive value of the 102 T allele is only 0.57 (confidence interval (CI) = 0.54–0.60), while the negative predictive value of lacking the T allele (the 102 C/C genotype) is only 0.54 (CI = 0.49–0.60) (Arranz et al., 1998) (see Table 2). Likewise, using the most generous estimate based on the meta-analysis data and the subsequent positive study, the positive predictive value of the 452His/His genotype is only 0.57 (CI = 0.56–0.59), while the negative predictive value of one or more copies of the 452Tyr allele is only 0.57 (CI = 0.46–0.62) (see Table 3). Based on only 13 subjects observed across studies, the negative predictive value of the 452Tyr/Tyr genotype is 0.85 (CI = 0.54–0.97) (Arranz et al., 1998; Masellis et al., 1998). Furthermore, the predicted population frequency of the 452Tyr/Tyr genotype is approximately 1% (Ozaki et al., 1997), which alone is not likely to justify screening. A recent extensive review of the pharmacogenetics of clozapine response is recommended (Masellis et al., 2000).

Table 2
Predictive value of *HTR2A* 102 T/C polymorphism in clozapine response

Genotype	Response	Nonresponse	Predictive value	Confidence interval
102 C/C	107	127	0.54	0.49–0.60
102 T/C or T/T	245	184	0.57	0.54–0.60

Table 3
Predictive value of HTR2A 452His/Tyr polymorphism in clozapine response

Genotype	Response	Nonresponse	Predictive value	Confidence interval
452His/His	402	301	0.57	0.56–0.59
452His/Tyr	65	76	0.54	0.46–0.62
452Tyr/Tyr	2	11	0.85	0.54–0.97
452Tyr	67	87	0.57	0.49–0.64

Lithium response has long been thought to have a genetic component (Grof et al., 1994; Morabito et al., 1982; Smeraldi et al., 1984). Given this belief and the implication of the serotonin system in mood disorders, one exploratory study has addressed the impact of *HTR2A* polymorphisms on response to lithium prophylaxis in mood disorders. Serretti et al. (2000) found no association between response to lithium prophylaxis and the 102 T/C or 1421 C/T polymorphisms in an Italian case-controlled sample.

While *HTR2A* variation may be an important determinant of response to certain serotonergic agents, further studies are clearly needed to better understand its involvement. If association between clozapine response and the 102 C allele is replicated, this likely reflects linkage disequilibrium with a nearby, as yet undiscovered, functional variant of *HTR2A*. While there is some evidence that the 452Tyr allele may have functional significance, this needs further study. These association studies must be viewed as preliminary; even if replicated, the findings will likely only achieve clinical utility in conjunction with additional genotyping.

3.4. 5-HT_{2C} receptor

The 5-HT_{2C} receptor is a post-synaptic G protein-linked receptor that activates both guanylyl cyclase and phosphoinositide hydrolysis (Kaufman et al., 1995). Some of the interest in this receptor centers on its possible role in hallucinations, for, as is the case for the 5-HT_{2A} receptor, LSD and clozapine have relatively high affinity for the 5-HT_{2C} receptor. Meltzer (1999) points out a relationship between atypical antipsychotic drug affinity for the 5-HT_{2C}

receptor and potential to produce weight gain. Indeed, the *5HT2C* knockout mouse is overweight, with a diminished response to the satiating effects of the 5-HT releaser D-fenfluramine (Tecott et al., 1995; Vickers et al., 1999). The *HTR2C* knockout mouse also shows an increased susceptibility to both spontaneous and chemically induced seizures (Tecott et al., 1995). Finally, animal research has stimulated interest in the 5-HT_{2C} receptor in alcoholism. In comparison with their counterparts, alcohol-preferring rats have been reported to have a higher density of 5-HT_{2C} receptors in certain brain regions, including the choroid plexus (Pandey et al., 1996).

A number of polymorphisms have been identified within the human 5-HT_{2C} receptor gene (*HTR2C*) located on chromosome Xq24. Only one amino acid variant has been identified, Cys23Ser, with the less common 23Ser allele having a population frequency of about 13% (Lappalainen et al., 1995). Lappalainen et al. (1995) report no difference in the concentration–response curves seen for 5-HT-induced cyclase activation when Xenopus oocytes expressing the two variants of the receptor were compared. On the other hand, Lappalainen et al. (1999) report higher cerebrospinal fluid (CSF) concentrations of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) in individuals with the 23Ser allele, in comparison with 23Cys/Cys homozygotes. They observed no changes in the CSF concentrations of serotonin or dopamine metabolites.

Various polymorphisms have also been reported outside of the coding region of *HTR2C*. A number of these reside within the promoter region, including a −1027(GT) repeat polymorphism and three single nucleotide polymorphisms: −995 G/A, −759 C/T, and −697 G/C. When transfected into a mouse embryonal carcinoma cell line, two haplotypes of promoter polymorphisms had significantly higher (1.44- and 2.58-fold elevations) promoter activity than the most common haplotype [$-1027(GT)_{17}$, −995 G, −759 C, −697 G] (Yuan et al., 2000). Further characterization of the *HTR2C* promoter region may clarify how these polymorphisms affect function. Postmortem studies or in vivo protein imaging studies using positron–emission tomography may reveal the impact of these promoter variants on gene expression in the human.

While *HTR2C* is of obvious interest in relation to a number of phenotypes including schizophrenia and obesity, no family-based disorder association studies have been reported. As mentioned, genetic studies of alcoholism and substance abuse combine aspects of disorder association and pharmacogenetic approaches. Only a few such studies are available regarding *HTR2C:* in Finnish, Japanese and United States samples, investigators have found no association between the Cys23Ser polymorphism and alcoholism (Himei et al., 2000; Lappalainen et al., 1999; Schuckit et al., 1999). Given the relatively low frequency of the 23Ser allele, family-based investigation of other polymorphisms, particularly those identified in the promoter region, is necessary to consider more fully *HTR2C* as a candidate in alcohol dependence.

As was true of *HTR2A*, initial pharmacogenetic studies of *HTR2C* have focused on clozapine response. Given that *HTR2C* is located on the X chromosome, one might expect to see gender differences in clozapine response; however this has not been reported. The studies focusing on *HTR2C* and clozapine response have assessed association using case-controlled design. Masellis et al. (1998) have noted a significant difference in allele frequency between Caucasian and African–American subjects. Sodhi et al. (1995) reported a strong association between the 23Ser allele and good response to clozapine in a population of Western European patients. Rietschel et al. (1997) report a non-significant trend toward association between 23Ser and clozapine response in a retrospective analysis of treatment results in German patients. Masellis et al. (1998) also report a non-significant trend toward association between the 23Ser allele and good response to 6 months of clozapine treatment in a population of United States Caucasian patients. Arranz et al. (2000a,b) likewise report a non-significant trend toward association with the 23Ser allele and retrospectively assessed response to clozapine in a population of British Caucasian subjects (Arranz et al., 2000b). On the other hand, Malhotra et al. (1996) found a non-significant trend in the opposite direction using a different approach. They compared subjects' response to 10 weeks of clozapine vs. their response to 4 weeks of treatment with a typical neuroleptic. As opposed to most of the studies on clozapine response, which used subjects resistant to or intolerant of treatment with other antipsychotic medication, Malhotra and colleagues selected a general sample of patients with schizophrenia or schizoaffective disorder, with unspecified ethnic background.

Given observed trends toward association between the 23Ser allele and response to clozapine in three of the studies that failed to find significance, we undertook a preliminary meta-analysis of the four studies that report genotype frequencies in the clozapine response and non-response groups (see Table 4). Since *HTR2C* is located on chromosome X and the original association was by allele, rather than genotype, we grouped subjects with one or

Table 4
Meta-analysis of association studies on *HTR2C* Cys23Cer in clozapine response

	Response to clozapine		Nonresponse to clozapine	
Association study	Cys only	Ser	Cys only	Ser
Sodhi et al. (1995)	84	19	57	2
Malhotra et al. (1996)	15	3	35	13
Rietschel et al. (1997)	59	19	63	11
Masellis et al. (1998)	55	17	58	9
Total subjects	213	58	213	35

$\chi^2 = 4.68$, 1 *df*, two-sided $P = 0.031$.

more copies of the 23Ser allele, including females with both 23Ser/Ser and 23Cys/Ser genotypes. Our simple meta-analysis reveals a significant case-controlled association across populations ($\chi^2 = 4.68$, 1 *df*, $P = 0.031$, two-sided), but this finding remains only exploratory until replicated using family- or genome-based control methods.

Arranz et al. (2000a,b) report a positive case-controlled association between a −330 GT/−244 CT repeat polymorphism and retrospective clozapine response (Arranz et al., 2000b). This association exists at the $P = 0.04$ level only when the short allele is considered dominant. Given the need for Bonferroni adjustment in their analysis of 19 polymorphisms in this subject sample, this result must be considered quite tenuous. In a preliminary case-controlled study addressing the impact of *HTR2C* polymorphisms on response to lithium prophylaxis in mood disorders, Serretti et al. (2000) found no significant association between response to lithium prophylaxis and the Cys23Ser polymorphism in an Italian sample.

Taken together, the case-controlled association studies of *HTR2C* polymorphisms suggest that this gene may be involved in response to clozapine. These exploratory studies need to be followed up by family-controlled association studies to further evaluate the possible role of this gene. If the specific promoter polymorphisms can be shown to have a functional role in gene expression, these variants are prime candidates for evaluation of *HTR2C* influence on response to clozapine and related medications.

3.5. 5-HT_{5A} receptor

Much less attention has been given to the 5-HT_{5A} receptor than the others that we have considered. 5-HT_{5A} receptor gene knockout mice show increased exploratory behavior in novel environments (Grailhe et al., 1999). LSD, which binds with high affinity to the 5-HT_{5A} receptor and typically provokes an increase in exploratory activity, has less effect in the knockout mice. No family-based disorder association studies have tested polymorphisms in the human 5-HT_{5A} receptor gene (*HTR5A*, located on chromosome 7q36.1). Birkett et al. (2000) found no association using a case-controlled design examining two single nucleotide polymorphisms and clozapine response in a population of British Caucasian schizophrenic subjects. Further exploration of possible gene variants is needed before the role of *HTR5A* in treatment response can be meaningfully evaluated.

3.6. 5-HT_{1A} receptor

The 5-HT_{1A} receptor, found both pre- and post-synaptically, is a G protein-linked receptor that acts primarily via inhibition of adenylyl cyclase (see Raymond et al. (1999) for a review of 5-HT_{1A} signal transduction). Much of the interest in this receptor centers on its possible involvement in the pathogenesis and treatment of anxiety and depression. 5-HT_{1A} receptor partial agonists such as buspirone have anxiolytic and antidepressant properties (De Vry, 1995) and the mixed β-adrenoceptor and 5-HT_{1A} receptor antagonist pindolol may decrease the latency to response or augment the antidepressant effect of specific serotonin reuptake inhibitors (McAskill et al., 1998). 5-HT_{1A} receptor gene knockout mice exhibit increased anxiety as indicated by decreased exploratory activity in multiple paradigms (Heisler et al., 1998; Parks et al., 1998; Ramboz et al., 1998). Interestingly, this anxiety responds poorly to benzodiazepines, and these mice have decreased $GABA_A$ receptor binding within the limbic system (Sibille et al., 2000). This ties together the serotonergic and GABAergic pathways, the two systems most frequently addressed by current anxiolytic therapies. Additionally, the 5-HT_{1A} receptor gene knockout mice exhibit some responses that are typically seen with antidepressant treatment: decreased immobility in both the forced swim test and in the tail suspension test (Heisler et al., 1998; Ramboz et al., 1998).

A number of polymorphisms, including several amino acid variants, have been identified within the human 5-HT_{1A} receptor gene (*HTR1A*) located on chromosome 5q11.2-13. Functional analyses have been performed on two of the amino acid variants. Rotondo et al. (1997) found no effect of the Gly22Ser variant on receptor binding profiles; however they did find that the rare 22Ser variant (0.2% in a Finnish population) was relatively insensitive to receptor down-regulation (Nakhai et al., 1995; Rotondo et al., 1997). In a study of the rare Ile28Val variant (0.55% in Finnish and American Caucasians), no differences in receptor concentration–response curves or ligand specificity were seen between cells expressing the two variants (Bruss et al., 1995; Nakhai et al., 1995).

The 5-HT_{1A} receptor gene should be considered a prime candidate gene in pharmacogenetics. The role of buspirone and other partial agonists in the treatment of anxiety suggests family-based studies of *HTR1A* polymorphisms are warranted. The resistance of the 5-HT_{1A} receptor gene knockout mouse to the effects of benzodiazepines should serve to further stimulate research on *HTR1A* variants in anxiety. The ability of pindolol to shorten the latency of response to selective serotonin reuptake inhibitors, presumably through its antagonism of somatodendritic 5-HT_{1A} recptors, also argues for study of *HTR1A* in selective serotonin reuptake inhibitor response. Unfortunately, most of the 5-HT_{1A} amino acid variants, even if they create functional changes in the protein, exist in the population at such low frequencies that they are unlikely to prove useful in clinical decision-making. To date, there have been no published family-based disorder association and linkage studies studying *HTR1A* polymorphisms. In studies at the University of Chicago, no association was observed between a single nucleotide polymorphism in the 5′ flanking region of *HTR1A* and autistic disorder using the TDT (Hoop and Cook, unpublished observation).

3.7. 5-HT_{1B} receptor

The 5-HT_{1B} receptor is a primarily presynaptic G protein-linked receptor that acts principally through adenylyl cyclase. Interest in this receptor has been focused on three separate areas. First, the 5-HT_{1B} receptor appears important in migraine headaches. The 5-HT_{1B} receptor is expressed in cerebral arteries, and 5-HT_{1B} receptor agonists promote vasoconstriction (Nilsson et al., 1999). Commonly used anti-migraine drugs, including sumatriptan and related compounds, are selective 5-HT_{1B} and 5-HT_{1D} receptor agonists (Deleu and Hanssens, 2000; Peroutka and McCarthy, 1989). Second, the 5-HT_{1B} receptor appears to play a role in aggression and substance abuse. 5-HT_{1B} receptor gene knockout mice displayed increased baseline activity and exploratory behavior, and increased aggressive response to intruders (Brunner et al., 1999; Malleret et al., 1999; Saudou et al., 1994); knockout animals also exhibited elevated alcohol consumption and increased cocaine-seeking behavior (Crabbe et al., 1996; Rocha et al., 1998). Furthermore, activation of the 5-HT_{1B} receptor in rats lowers ethanol self-administration (Tomkins and O'Neill, 2000). Quantitative trait locus (QTL) linkage mapping studies have identified alcohol preference and morphine sensitivity loci near the mouse 5-HT_{1B} receptor gene (Belknap et al., 1995; Crabbe et al., 1994). Finally, like 5-HT_{2C} gene knockouts, 5-HT_{1B} knockout mice are insensitive to the anorectic effects of fenfluramine (Lucas et al., 1998).

A number of polymorphisms have been identified within the 5-HT_{1B} receptor gene (*HTR1B*) located on chromosome 6q13. One of these, Phe124Cys, causes a rare phenyalanine to cysteine amino acid change. Bruss et al. (1999) found higher affinity of various receptor ligands for the 5-HT_{1B} receptor 124Cys variant expressed in COS-7 cells. Although several other single nucleotide polymorphisms have been identified within *HTR1B*, their functional significance has not been examined.

Preliminary family-based studies have investigated *HTR1B* in various psychiatric and alcoholism phenotypes. Mundo et al. (2000a) found association and linkage by TDT between obsessive–compulsive disorder and the 861 C allele at an 861 G/C single nucleotide polymorphism in a population of Canadian subjects. Lappalainen et al. (1998) used sib pair analysis in sets of Finnish subjects and Native American subjects to test for linkage between antisocial alcoholism and *HTR1B*. They found significant linkage in both groups at the 861 G/C single nucleotide polymorphism within *HTR1B*. Additionally, they reported association between the 861 C allele and antisocial alcoholism within the Finnish subjects. Animal studies also suggest a role for the 5-HT_{1B} receptor in the pharmacogenetics of substance use. Hain et al. (1999) tested the ability of the 5-HT_{1B} receptor antagonist GR127935 to antagonize the effects of morphine in two strains of rats and found that GR127935 causes a dose-dependent antagonism of the analgesic effects of morphine only in the high morphine-sensitivity strain.

Variation in the 5-HT_{1B} receptor may be important in determining response to drugs of abuse, but the specific variants involved have yet to be discovered. The animal data and the linkage finding with antisocial alcoholism in the humans may point to a functional polymorphism within the promoter or enhancer regions of *HTR1B*. The role of any functional *HTR1B* variants in the pathogenesis and treatment of substance abuse, migraine, and anxiety remains an open and intriguing question.

3.8. The serotonin transporter

The serotonin transporter protein (5-HTT) acts as the primary mechanism of removing 5-HT from the synaptic cleft. It is the target of the 5-HT reuptake inhibitors that are widely used to treat depression and are uniquely efficacious in treating obsessive–compulsive disorder. The drugs potently inhibiting 5-HT transport include the selective serotonin reuptake inhibitors fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram, as well as the less selective tricyclic antidepressant clomipramine. Postmortem 5-HTT binding is lower in the ventral prefrontal cortex of suicides and lower throughout the prefrontal cortex of subjects with a history of depression (Mann et al., 2000). A knockout mouse lacking the serotonin transporter gene (*HTT*) has no obvious developmental abnormalities (Bengel et al., 1998), although diminished 5-HT concentration within various brain regions, as well as changes in distribution and density 5-HT_{1A} and 5-HT_{2A} receptors, have been observed (Bengel et al., 1998; Li et al., 1999; Rioux et al., 1999). As expected, the knockout mouse shows no locomotor stimulatory response to MDMA ("ecstasy"), which releases 5-HT via a transporter-dependent mechanism (Bengel et al., 1998).

Two interesting polymorphisms have been identified within the human serotonin transporter gene (*HTT*) located on chromosome 17q11.1-q12. One, a variable number of tandem repeats (VNTR) polymorphism located in the *HTT* promoter region has been the subject of intense study since it was first reported to differentially affect gene expression (Heils et al., 1996; Lesch et al., 1996). Two alleles are expressed most prominently: the short allele (s) corresponds to 14 copies of the 20–23 bp repeat unit, while the long allele (l) contains 16 copies. The long allele appears to be a more effective promoter within cell transfection models, with approximately 2-fold greater expression for the l/l genotype in comparison with the l/s or s/s genotypes (Heils et al., 1996; Lesch et al., 1996). Human postmortem brain and in vivo neuroimaging studies have found higher midbrain 5-HTT binding in subjects with the l/l genotype (Heinz et al., 2000; Little et al., 1998), but this was not found with prefrontal cortex 5-HTT binding (Mann et al., 2000).

A second VNTR polymorphism has also been described within intron 2 of *HTT*. Consisting of 9, 10, or 12 copies of a 16–17 bp repeat element, this VNTR has been recently shown to have potential transcription enhancer effects. Fiskerstrand et al. (1999) found increased expression in promoter-driven reporter gene constructs containing 12 repeats, in comparison to those with 10 repeats. MacKenzie and Quinn (1999) produced transgenic mice with the VNTR enhancer region introduced into a reporter gene. They noted increased expression levels in the vicinity of the dorsal raphe nucleus during embryonic development in 12-repeat mice when compared to 10-repeat animals. This observation may point to a role for the intron 2 VNTR in brain development in addition to its possible role in the mature synapse. While these two VNTR polymorphisms have both been shown to differentially affect gene expression, the possibility remains that there are other additional polymorphisms affecting transcription of this gene.

The promoter VNTR has been studied in numerous psychiatric disorders. The initial association reported was between the s allele and neuroticism in case-controlled analysis that was supported by within-family sibling-pairs analysis (Lesch et al., 1996). This association was replicated twice using similar separate case-controlled association and sib-pair samples in Israel and in Japan (Hu et al., 2000; Osher et al., 2000) and a Finnish replication found linkage, but not association, in a sib-pair sample (Mazzanti et al., 1998). After a mixture of support and non-support was found in a number of case-controlled studies, Gelernter et al. (1999) clearly demonstrated the need for family-based methodology by showing dramatic differences in allele frequencies across populations. Substantial differences were seen between two "European" populations, the Danes and the Russian Adygei. Analysis of extended haplotypes incorporating additional polymorphisms may help to clarify whether any given polymorphism is responsible for the genetic contribution of serotonin transporter gene variants to specific phenotypes.

In autistic disorder, Cook et al. (1997) initially reported association with a haplotype including the promoter VNTR s allele. One subsequent study found linkage disequilibrium with the l allele in a German population, and a study of French individuals found only a trend toward an association with the l allele (Cook et al., 1997; Klauck et al., 1997; Tordjman et al., 2001), although others have found no significant linkage disequilibrium (Maestrini et al., 1999; Persico et al., 2000). When studying a possible allelic influence on severity within domains of autistic behavior, Tordjman et al. (2001) found greater transmission of the l allele in less severely socially and communicationally affected subgroups.

In obsessive–compulsive disorder, one family-based study found association in the presence of linkage with the l allele (McDougle et al., 1998). Four family-based studies in adult bipolar disorder and one in childhood-onset bipolar disorder found no significant association (Bocchetta et al., 1999; Esterling et al., 1998; Geller and Cook, 1999; Kirov et al., 1999; Mundo et al., 2000b).

A more limited number of family-based studies have examined possible disorder association with the intron 2 VNTR. Following multiple positive and negative case-controlled association studies in bipolar disorder, one family-based study found no significant association or linkage in bipolar disorder using TDT and sib-pair analysis (Esterling et al., 1998). In schizophrenia, Hranilovic et al. (2000) found significant association in the presence of linkage with allele 12 in families having multiple siblings affected by schizophrenia or schizoaffective disorder.

In the substance abuse area, Hu et al. (2000) studied the interaction of the *HTT* promoter VNTR and neuroticism in smoking cessation. Using a case-controlled analysis, they found that neuroticism was linked with nicotine dependence only in the subgroup of subjects with at least one copy of the s allele. A follow-up discordant genotype sib-pair analysis revealed a non-significant trend for association between neuroticism and current smoking in the subgroup of siblings with the s allele. Strengthening the initial case-controlled finding is a replication in a separate sample showing that for subjects with at least one s allele, neuroticism was associated with nicotine dependence, smoking to reduce negative mood, and smoking for stimulation (Lerman et al., 2000). While these studies need to be replicated using family-based designs, they suggest the possibility that, in the future, differential smoking cessation treatments might be choosen based on *HTT* genotypes.

The data on the *HTT* promoter VNTR in alcohol abuse and dependence remains incomplete. Edenberg et al. (1998) performed the only family-based study of the serotonin transporter gene in alcohol dependence. Using a TDT design in United States families with at least three affected relatives, no significant association was seen between either major allele of the promoter VNTR and alcohol dependence or withdrawal-related symptoms. There are multiple ways of assessing severity and variation within alcohol abuse and dependence, including subtyping alcoholics by personality characteristics (Cloninger, 1987). A number of case-controlled trials with various designs have found association between different alleles of the promoter VNTR and alcohol dependence in different populations (Ishiguro et al., 1999a; Sander et al., 1997, 1998; Schuckit et al., 1999; Turker et al., 1998). Family-based studies focusing on patients with alcoholism fitting a particular personality profile will assist in interpretation of the current findings.

Another line of inquiry has focused directly on brain expression of the serotonin transporter protein in alcohol-dependent subjects with various genotypes at the promoter VNTR polymorphism. Little et al. (1998) performed a case-controlled study aimed at the interaction between genotype and alcohol use on postmortem brain transporter

binding sites. In those subjects with one or more copies of the s allele, ethanol-using individuals had significantly higher postmortem dorsal raphe 5-HTT binding than their control counterparts. In contrast, 5-HTT binding sites did not differ across ethanol users and controls for subjects with the l/l genotype. Dissimilar results were obtained by Heinz et al. (2000) when examining the relationship between promoter genotype and in vivo 5-HTT expression using single photon emission computerized tomography imaging of the raphe area in male alcoholics. They found that l/l genotype alcoholics showed a significant reduction in 5-HTT binding sites in comparison with l/l genotype controls; no such difference was seen in subjects with one or more copies of the s allele. Using covariate analysis, they found that accounting for lifetime alcohol consumption eliminated this effect. The authors hypothesize that this reduction could be due to a differential toxic effect of alcohol on raphe neurons in subjects with the l/l genotype. As they note, alcohol withdrawal 3 weeks prior to the study may have confounded the results.

Two exploratory studies have used case-controlled association methods to study the serotonin transporter gene in heroin dependence. Tan et al. (1999) found an association between heroin dependence and allele 10 of the intron 2 VNTR, but no association with the promoter VNTR. Another heroin case-controlled study also found no association with the promoter polymorphism (Kotler et al., 1999).

Since the serotonin transporter is the target for the selective serotonin reuptake inhibitors, as well as the antidepressant clomipramine, the effect of the *HTT* variants on clinical response to these drugs is of great interest. Until recently, there have been only hints suggesting more homogeneous response to antidepressants within families (Franchini et al., 1998; O'Reilly et al., 1994). These hints at familiality may reflect genetic variation in metabolism of these drugs (which has been documented, see Bertilsson et al. (1997) for a review), genetic variation within the serotonin system itself, or a combination of genetically determined pharmacokinetic and pharmacodynamic effects.

Initial studies directly studying the pharmacogenetic effects of *HTT* variants have thus far utilized case-controlled methods and have generated disparate results in different populations. Smeraldi et al. (1998) studied the effects of the promoter VNTR polymorphism on clinical response to fluvoxamine in Italian patients with bipolar or unipolar delusional depression. Subjects with one or more copies of the l allele showed significantly greater improvement in Hamilton Depression Rating Scale (HDRS) scores than did subjects with the s/s genotype. The same group replicated this initial finding using paroxetine in Italian patients with non-delusional unipolar depression (Zanardi et al., 2000). On the other hand, Kim et al. (2000) showed an association in the opposite direction in a Korean population of patients with a unipolar major depressive episode. They compared responders (subjects having a greater than 50% decrease in HDRS score) to nonresponders, and found that the s/s genotype was significantly more frequent among responders than among nonresponders. They also found significant association between specific serotonin reuptake inhibitor response and the intron 2 VNTR 12/12 genotype. If these findings persist in family-based studies, the strong associations with opposite alleles in different homogeneous populations may reflect linkage of these polymorphisms to an additional variant important in gene regulation (Allison, 1997).

Although the selective serotonin reuptake inhibitors are widely used to treat depression, they have also been found to be useful in the treatment of obsessive–compulsive disorder, social phobia, anxiety, and autism. Genetic effects on specific serotonin reuptake inhibitor treatment response is, thus, of interest in a range of psychiatric symptoms and disorders. However, at present, there are only two studies outside the depression field; these both found no association between *HTT* genotype and specific serotonin reuptake inhibitor response in obsessive–compulsive disorder (Billett et al., 1997; McDougle et al., 1998). Going further afield, the study of healthy subjects may provide a route to understanding the role of these variants in the normally functioning serotonin system. In this vein, Whale et al. (2000) studied the impact of *HTT* promoter VNTR genotype on acute prolactin response following clomipramine administration to normal controls and found significantly higher prolactin response in subjects with the l/l genotype.

These studies examining both long-term and short-term response to specific serotonin reuptake inhibitors raise interesting questions regarding the therapeutic actions of these drugs. Smeraldi et al. (1998) and Whale et al. (2000) both suggest a crucial role for inhibitory 5-HT_{1A} autoreceptors in subjects with the s/s genotype. In theory, these subjects have fewer transporter sites that are more completely blocked by a given amount of specific serotonin reuptake inhibitor. The presumed greater immediate increase in extracellular 5-HT leads to greater activation of the inhibitory 5-HT_{1A} autoreceptors, and a greater and more long-lasting reduction in neuronal firing and 5-HT release. Smeraldi et al. (1998) tested this hypothesis by randomly assigning a subgroup of subjects to receive fluvoxamine plus pindolol, a 5-HT_{1A} receptor antagonist. Within the subjects who received pindolol, no difference was seen in response across genotypes, suggesting that, by blocking 5-HT_{1A}-mediated negative feedback, pindolol eliminates the effect of genotype. Whale et al. (2000) and Kelsoe (1998) suggest a simple (and diametrically opposed) alternative hypothesis: that a lower number of serotonin transporter sites may result in a lower capacity to boost extracellular 5-HT through transporter blockade. Additionally, the fixed doses of specific serotonin reuptake inhibitor used may have resulted in under- or over-treatment of subjects with different 5-HTT expression levels. Larger studies will help to clarify these issuses.

It should be noted that variants of *HTT* might affect mood elevation in a more general way. Benedetti et al. (1999) found an association between the l allele and mood elevation following sleep deprivation in a sample of Italian bipolar patients. Taken together with the studies showing better specific serotonin reuptake inhibitor response in l/s and l/l individuals, the finding suggests that *HTT* may play a central role in the modulation of mood, rather than simply affecting response to antidepressant therapy. As we discussed, however, known *HTT* variants have not been demonstrated to contribute to bipolar disorder susceptibility (Bocchetta et al., 1999; Esterling et al., 1998; Geller and Cook, 1999; Kirov et al., 1999; Mundo et al., 2000b).

As variation in 5-HTT receptor expression or function may influence 5-HT levels at all serotonin synapses, *HTT* variates may affect the response to almost any agent affecting the serotonin system. Investigators have started studying the relevance of *HTT* variants in the response seen for other classes of serotonergic agents. Using a case-controlled design, Arranz et al. (2000a) found no significant association between response to clozapine in a population of British schizophrenic subjects and any allele of the promoter or intron 2 VNTR polymorphisms. In another study, they found a significant association between the s/s genotype and poor response only when no Bonferroni correction was employed (Arranz et al., 2000b). These findings need to be replicated in an independent, family-based sample. A study examining the intron 2 VNTR and changes in mood following tryptophan depletion in patients with seasonal affective disorder found no significant association (Lenzinger et al., 1999).

The *HTT* variants discovered thus far are already providing hints of relevance to pharmacological response. While we are starting to understand their effects on the response to various drugs including nicotine, alcohol, and specific serotonin reuptake inhibitors, these variants may be found to have wide-ranging effects involving almost any therapy that affects the serotonin system. Given the known disparities in allele frequencies across populations, however, it will be particularly important to use family-based methods in future studies of these *HTT* variants in pharmacogenetics and to more thoroughly screen the gene for possible variation in different disorders. Conversely, differences noted in drug response profiles across ethnic groups may point to certain polymorphisms as likely candidates for pharmacogenetic investigation.

3.9. Monoamine oxidase-A

Monoamine oxidase-A preferentially catalyzes the oxidative deamination of serotonin and norepinephrine. Interest in monoamine oxidase-A has centered around two bodies of evidence. First, it may be involved in aggressive behavior, since males in a Dutch kindred with a point mutation in the monoamine oxidase-A gene display impulsive aggression (Brunner et al., 1993). Male monoamine oxidase-A gene knockout mice also show increased aggressive behavior, as well as elevated brain concentrations of 5-HT and norepinephrine (Cases et al., 1995). Second, it may be involved in depression and panic disorder, since monoamine oxidase inhibitors are frequently used to treat these disorders.

A number of polymorphisms have been described within the human monoamine oxidase-A gene (*MAOA*) located on chromosome Xp11.23-11.4. One of these, a 30-bp VNTR located within the promoter region, has been shown to affect gene expression. In transfection experiments, Sabol et al. (1998) found that greater gene expression was observed for 3.5- or 4-copy variants compared to 3- or 5-copy variants. Jonsson et al. (2000) found increased cerebrospinal fluid levels of 5-HIAA and homovanillic acid in women with one or more copy of the 3.5 or 4-repeat promoter allele; no such relationship was found among the men studied.

The only family-based study on the possible role of *MAOA* in a psychiatric phenotype examined a range of *MAOA* polymorphisms and found no association or linkage within a small sample of lithium-responsive bipolar disorder subjects (Turecki et al., 1999b). There have been a number of case-controlled association studies in alcoholism, but no consistent findings have emerged (Gade et al., 1998; Hsu et al., 1996; Samochowiec et al., 1999). The only study to address the role of the functional VNTR polymorphism in the *MAOA* promoter region found a case-controlled association with antisocial behavior in a group of alcoholic subjects (Samochowiec et al., 1999). Family-based association and linkage studies should clarify these results. Another logical next step would be pharmacogenetic studies of the effects of the functional promoter VNTR on response to monoamine oxidase inhibitors or other antidepressants.

4. Conclusions

The preliminary and oftentimes inconsistent nature of the data reviewed might seem discouraging. However, the studies represent the initial forays into what promises to be a rewarding frontier. As we gain an appreciation of the potential for polymorphisms in promoter and regulatory regions to impact gene expression, knowledge of new functional variants will emerge. Careful study of regulatory and coding variants should lead to the identification of genetic subgroups that respond more or less well to a given treatment. This pharmacogenetic profiling would enhance therapeutics immensely by improving rates and magnitudes of response, and allowing adverse effects to be minimized. The current studies within the serotonin system merely hint at the potential of pharmacogenetics; this first glimpse should motivate larger and more rigorous studies.

Several points can be made regarding future pharmacogenetics research on the serotonin system. First, a better

understanding of the genetic contribution to protein expression and psychiatric phenotype will emerge when a more complete picture of variation within each relevant gene becomes available. Second, as investigators seek to identify alleles that influence risk to (or severity of) neuropsychiatric disorders, the association studies need to utilize family-based or population-based control in order to prevent population stratification bias and admixture artifact (Bacanu et al., 2000; Ewens and Spielman, 1995; Pritchard et al., 2000; Spielman et al., 1993). Properly controlled and replicated disorder association studies should provide a number of alleles with a high likelihood of influencing pharmacological response in the disorder. Third, pharmacogenetic studies need to use randomized, double-blind clinical trial methodology and incorporate quantitative trait loci approaches when assessing genetic influences on drug response (Allison, 1997). However, even carefully conducted pharmacogenetic clinical trials may suffer from population stratification bias if they fail to utilize family or population-based controls (Drazen et al., 1999). In the case of population-based control, tests specifically targeting quantitative traits have yet to be devised, but consideration of drug response vs. non-response is possible. Fourth, the study of pharmacogenetics will evolve as more specific drugs are discovered. For example, the effects of *HTR2A* variants on response to a specific 5-HT_{2A} receptor antagonist will likely be more robust than the influence seen for the available, less specific, agents such as clozapine and other atypical neuroleptics.

The critical and manifold roles of the serotonin system, the great abundance of targets within the system, the wide range of serotonergic agents—available and in development—and the promising preliminary results suggest that the serotonin system offers a particularly rich area for pharmacogenetics research.

References

Aghajanian, G.K., Marek, G.J., 1999. Serotonin and hallucinogens. Neuropsychopharmacology 21, 16S–23S.

Allison, D.B., 1997. Transmission–disequilibrium tests for quantitative traits. Am. J. Hum. Genet. 60, 676–690.

Anderson, G.M., Cook, E.H., 2000. Pharmacogenetics: promise and potential in child and adolescent psychiatry. Child Adolescent Psychiat. Clin. North Am. 9, 23–42.

Arranz, M., Collier, D., Sodhi, M., Ball, D., Roberts, G., Price, J., Sham, P., Kerwin, R., 1995. Association between clozapine response and allelic variation in 5-HT2A receptor gene. Lancet 346, 281–282.

Arranz, M.J., Munro, J., Sham, P., Kirov, G., Murray, R.M., Collier, D.A., Kerwin, R.W., 1998. Meta-analysis of studies on genetic variation in 5-HT2A receptors and clozapine response. Schizophr. Res. 32, 93–99.

Arranz, M.J., Bolonna, A.A., Munro, J., Curtis, C.J., Collier, D.A., Kerwin, R.W., 2000a. The serotonin transporter and clozapine response. Mol. Psychiatry 5, 124–125.

Arranz, M.J., Munro, J., Birkett, J., Bolonna, A., Mancama, D., Sodhi, M., Lesch, K.P., Meyer, J.F., Sham, P., Collier, D.A., Murray, R.M., Kerwin, R.W., 2000b. Pharmacogenetic prediction of clozapine response. Lancet 355, 1615–1616.

Bacanu, S.-A., Devlin, B., Roeder, K., 2000. The power of genomic control. Am. J. Hum. Genet. 66, 1933–1944.

Belknap, J.K., Mogil, J.S., Helms, M.L., Richards, S.P., O'Toole, L.A., Bergeson, S.E., Buck, K.J., 1995. Localization to chromosome 10 of a locus influencing morphine analgesia in crosses derived from C57BL/6 and DBA/2 strains. Life Sci. 57, L117–L124.

Benedetti, F., Serretti, A., Colombo, C., Campori, E., Barbini, B., di Bella, D., Smeraldi, E., 1999. Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. Am. J. Psychiatry 156, 1450–1452.

Bengel, D., Murphy, D.L., Andrews, A.M., Wichems, C.H., Feltner, D., Heils, A., Mossner, R., Westphal, H., Lesch, K.P., 1998. Altered brain serotonin homeostasis and locomotor insensitivity to 3, 4-methylenedioxymethamphetamine ("Ecstasy") in serotonin transporter-deficient mice. Mol. Pharmacol. 53, 649–655.

Bertilsson, L., Dahl, M.L., Tybring, G., 1997. Pharmacogenetics of antidepressants: clinical aspects. Acta Psychiatr. Scand. Suppl. 391, 14–21.

Billett, E.A., Richter, M.A., King, N., Heils, A., Lesch, K.P., Kennedy, J.L., 1997. Obsessive compulsive disorder, response to serotonin reuptake inhibitors and the serotonin transporter gene. Mol. Psychiatry 2, 403–406.

Birkett, J.T., Arranz, M.J., Munro, J., Osbourn, S., Kerwin, R.W., Collier, D.A., 2000. Association analysis of the 5-HT5A gene in depression, psychosis and antipsychotic response. NeuroReport 11, 2017–2020.

Bocchetta, A., Piccardi, M.P., Palmas, M.A., Chillotti, C., Oi, A., Del Zompo, M., 1999. Family-based association study between bipolar disorder and DRD2, DRD4, DAT, and SERT in Sardinia. Am. J. Med. Genet. 88, 522–526.

Brunner, H., Nelen, M., Breakefield, X., Ropers, H., van Oost, B., 1993. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. Science 262, 578–580.

Brunner, D., Buhot, M.C., Hen, R., Hofer, M., 1999. Anxiety, motor activation, and maternal-infant interactions in 5HT1B knockout mice. Behav. Neurosci. 113, 587–601.

Bruss, M., Buhlen, M., Erdmann, J., Gothert, M., Bonisch, H., 1995. Binding properties of the naturally occurring human 5-HT1A receptor variant with the Ile28Val substitution in the extracellular domain. Naunyn-Schmiedeberg's Arch. Pharmacol. 352, 455–458.

Bruss, M., Bonisch, H., Buhlen, M., Nothen, M.M., Propping, P., Gothert, M., 1999. Modified ligand binding to the naturally occurring Cys-124 variant of the human serotonin 5-HT1B receptor. Pharmacogenetics 9, 95–102.

Cases, O., Seif, I., Grimsby, J., Gaspar, P., Chen, K., Pournin, S., Mueller, U., Aguet, M., Babinet, C., Shih, J.C., De Maeyer, E., 1995. Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. Science 268, 1763–1766.

Chaffee, B.J., Tankanow, R.M., 1991. Ondansetron—the first of a new class of antiemetic agents. Clin. Pharm. 10, 430–446.

Chennaoui, M., Grimaldi, B., Fillion, M.P., Bonnin, A., Drogou, C., Fillion, G., Guezennec, C.Y., 2000. Effects of physical training on functional activity of 5-HT1B receptors in rat central nervous system: role of 5-HT-moduline. Naunyn-Schmiedeberg's Arch. Pharmacol. 361, 600–604.

Cloninger, C.R., 1987. Neurogenetic adaptive mechanisms in alcoholism. Science 236, 410–416.

Cook, E., Leventhal, B., 1996. The serotonin system in autism. Curr. Opin. Pediatr. 8, 348–354.

Cook, E.H. Jr., Courchesne, R., Lord, C., Cox, N.J., Yan, S., Lincoln, A., Haas, R., Courchesne, E., Leventhal, B.L., 1997. Evidence of linkage between the serotonin transporter and autistic disorder. Mol. Psychiatry 2, 247–250.

Crabbe, J.C., Belknap, J.K., Buck, K.J., 1994. Genetic animal models of alcohol and drug abuse. Science 264, 1715–1723.

Crabbe, J.C., Phillips, T.J., Feller, D.J., Hen, R., Wenger, C.D., Lessov, C.N., Schafer, G.L., 1996. Elevated alcohol consumption in null mutant mice lacking 5-HT1B serotonin receptors. Nat. Genet. 14, 98–101.

De Vry, J., 1995. 5-HT1A receptor agonists: recent developments and controversial issues. Psychopharmacology (Berl.) 121, 1–26.

Deckert, J., Catalano, M., Syagailo, Y.V., Bosi, M., Okladnova, O., Di Bella, D., Nothen, M.M., Maffei, P., Franke, P., Fritze, J., Maier, W., Propping, P., Beckmann, H., Bellodi, L., Lesch, K.P., 1999. Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. Hum. Mol. Genet. 8, 621–624.

Deleu, D., Hanssens, Y., 2000. Current and emerging second-generation triptans in acute migraine therapy: a comparative review. J. Clin. Pharmacol. 40, 687–700.

Drazen, J.M., Yandava, C.N., Dube, L., Szczerback, N., Hippensteel, R., Pillari, A., Israel, E., Schork, N., Silverman, E.S., Katz, D.A., Drajesk, J., 1999. Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. Nat. Genet. 22, 168–170.

Edenberg, H.J., Reynolds, J., Koller, D.L., Begleiter, H., Bucholz, K.K., Conneally, P.M., Crowe, R., Goate, A., Hesselbrock, V., Li, T.K., Nurnberger, J.I. Jr., Porjesz, B., Reich, T., Rice, J.P., Schuckit, M., Tischfield, J.A., Foroud, T., 1998. A family-based analysis of whether the functional promoter alleles of the serotonin transporter gene HTT affect the risk for alcohol dependence. Alcohol Clin. Exp. Res. 22, 1080–1085.

Erdmann, J., Shimron-Abarbanell, D., Rietschel, M., Albus, M., Maier, W., Koerner, J., Bondy, B., Chen, K., Shih, J.C., Knapp, M., Propping, P., Noethen, M.M., 1996. Systematic screening for mutations in the human serotonin-2A (5-HT2A) receptor gene: identification of two naturally occurring receptor variants and association analysis in schizophrenia. Hum. Genet. 97, 614–619.

Esterling, L.E., Yoshikawa, T., Turner, G., Badner, J.A., Bengel, D., Gershon, E.S., Berrettini, W.H., Detera-Wadleigh, S.D., 1998. Serotonin transporter (5-HTT) gene and bipolar affective disorder. Am. J. Med. Genet. 81, 37–40.

Ewens, W., Spielman, R., 1995. The transmission/disequilibrium test: History, subdivision, and admixture. Am. J. Hum. Genet. 57, 455–464.

Fiskerstrand, C.E., Lovejoy, E.A., Quinn, J.P., 1999. An intronic polymorphic domain often associated with susceptibility to affective disorders has allele dependent differential enhancer activity in embryonic stem cells. FEBS Lett. 458, 171–174.

Franchini, L., Serretti, A., Gasperini, M., Smeraldi, E., 1998. Familial concordance of fluvoxamine response as a tool for differentiating mood disorder pedigrees. J. Psychiatr. Res. 32, 255–259.

Frishman, W.H., Grewall, P., 2000. Serotonin and the heart. Ann. Med. 32, 195–209.

Gade, R., Muhleman, D., Blake, H., MacMurray, J., Johnson, P., Verde, R., Saucier, G., Comings, D.E., 1998. Correlation of length of VNTR alleles at the X-linked MAOA gene and phenotypic effect in Tourette syndrome and drug abuse. Mol. Psychiatry 3, 50–60.

Gelernter, J., Cubells, J.F., Kidd, J.R., Pakstis, A.J., Kidd, K.K., 1999. Population studies of polymorphisms of the serotonin transporter protein gene. Am. J. Med. Genet. 88, 61–66.

Geller, B., Cook, E., 1999. Serotonin transporter gene (HTTLPR) is not in linkage disequilibrium with prepubertal and early adolescent bipolarity. Biol. Psychiatry 45, 1230–1233.

Glennon, R.A., Titeler, M., McKenney, J.D., 1984. Evidence for 5-HT2 involvement in the mechanism of action of hallucinogenic agents. Life Sci. 35, 2505–2511.

Grailhe, R., Waeber, C., Dulawa, S.C., Hornung, J.P., Zhuang, X., Brunner, D., Geyer, M.A., Hen, R., 1999. Increased exploratory activity and altered response to LSD in mice lacking the 5-HT(5A) receptor. Neuron 22, 581–591.

Grimaldi, B., Bonnin, A., Fillion, M.P., Prudhomme, N., Fillion, G., 1999. 5-Hydroxytryptamine-moduline: a novel endogenous peptide involved in the control of anxiety. Neuroscience 93, 1223–1225.

Grof, P., Alda, M., Grof, E., Zvolsky, P., Walsh, M., 1994. Lithium response and genetics of affective disorders. J. Affect. Disord. 32, 85–95.

Hain, H.S., Belknap, J.K., Mogil, J.S., 1999. Pharmacogenetic evidence for the involvement of 5-hydroxytryptamine (serotonin)-1B receptors in the mediation of morphine antinociceptive sensitivity. J. Pharmacol. Exp. Ther. 291, 444–449.

Hawi, Z., Myakishev, M.V., Straub, R.E., O'Neill, A., Kendler, K.S., Walsh, D., Gill, M., 1997. No association or linkage between the 5-HT2a/T102C polymorphism and schizophrenia in Irish families. Am. J. Med. Genet. 74, 370–373.

Heils, A., Teufel, A., Petri, S., Stoeber, G., Riederer, P., Bengel, D., Lesch, K.P., 1996. Allelic variation of human serotonin transporter gene expression. J. Neurochem. 66, 2621–2624.

Heinz, A., Jones, D.W., Mazzanti, C., Goldman, D., Ragan, P., Hommer, D., Linnoila, M., Weinberger, D.R., 2000. A relationship between serotonin transporter genotype and in vivo protein expression and alcohol neurotoxicity. Biol. Psychiatry 47, 643–649.

Heisler, L.K., Chu, H.M., Brennan, T.J., Danao, J.A., Bajwa, P., Parsons, L.H., Tecott, L.H., 1998. Elevated anxiety and antidepressant-like responses in serotonin 5-HT1A receptor mutant mice. Proc. Natl. Acad. Sci. U. S. A. 95, 15049–15054.

Himei, A., Kono, Y., Yoneda, H., Sakai, T., Koh, J., Sakai, J., Inada, Y., Imamichi, H., 2000. An association study between alcoholism and the serotonergic receptor genes. Alcohol Clin. Exp. Res. 24, 341–342.

Hranilovic, D., Schwab, S.G., Jernej, B., Knapp, M., Lerer, B., Albus, M., Rietschel, M., Kanyas, K., Borrmann, M., Lichtermann, D., Maier, W., Wildenauer, D.B., 2000. Serotonin transporter gene and schizophrenia: evidence for association/linkage disequilibrium in families with affected siblings. Mol. Psychiatry 5, 91–95.

Hsu, Y.P., Loh, E.W., Chen, W.J., Chen, C.C., Yu, J.M., Cheng, A.T., 1996. Association of monoamine oxidase A alleles with alcoholism among male Chinese in Taiwan. Am. J. Psychiatry 153, 1209–1211.

Hu, S., Brody, C.L., Fisher, C., Gunzerath, L., Nelson, M.L., Sabol, S.Z., Sirota, L.A., Marcus, S.E., Greenberg, B.D., Murphy, D.L., Hamer, D.H., 2000. Interaction between the serotonin transporter gene and neuroticism in cigarette smoking behavior. Mol. Psychiatry 5, 181–188.

Ishiguro, H., Saito, T., Akazawa, S., Mitushio, H., Tada, K., Enomoto, M., Mifune, H., Toru, M., Shibuya, H., Arinami, T., 1999a. Association between drinking-related antisocial behavior and a polymorphism in the serotonin transporter gene in a Japanese population. Alcohol Clin. Exp. Res. 23, 1281–1284.

Ishiguro, H., Saito, T., Shibuya, H., Toru, M., Arinami, T., 1999b. The 5′ region of the tryptophan hydroxylase gene: mutation search and association study with alcoholism. J. Neural Transm. 106, 1017–1025.

Jonsson, E.G., Norton, N., Gustavsson, J.P., Oreland, L., Owen, M.J., Sedvall, G.C., 2000. A promoter polymorphism in the monoamine oxidase A gene and its relationships to monoamine metabolite concentrations in CSF of healthy volunteers. J. Psychiatr. Res. 34, 239–244.

Kang, A.M., Palmatier, M.A., Kidd, K.K., 1999. Global variation of a 40-bp VNTR in the 3′-untranslated region of the dopamine transporter gene (SLC6A3). Biol. Psychiatry 46, 151–160.

Kaufman, M.J., Hartig, P.R., Hoffman, B.J., 1995. Serotonin 5-HT2C receptor stimulates cyclic GMP formation in choroid plexus. J. Neurochem. 64, 199–205.

Kelsoe, J.R., 1998. Promoter prognostication: the serotonin transporter gene and antidepressant response. Mol. Psychiatry 3, 475–476.

Kim, D.K., Lim, S.W., Lee, S., Sohn, S.E., Kim, S., Hahn, C.G., Carroll, B.J., 2000. Serotonin transporter gene polymorphism and antidepressant response. NeuroReport 11, 215–219.

Kirov, G., Rees, M., Jones, I., MacCandless, F., Owen, M.J., Craddock, N., 1999. Bipolar disorder and the serotonin transporter gene: a family-based association study. Psychol. Med. 29, 1249–1254.

Klauck, S.M., Poustka, F., Benner, A., Lesch, K.-P., Poustka, A., 1997. Serotonin transporter (5-HTT) gene variants associated with autism? Hum. Mol. Genet. 6, 2233–2238.

Kotler, M., Cohen, H., Kremer, I., Mel, H., Horowitz, R., Ohel, N., Gritsenko, I., Nemanov, L., Katz, M., Ebstein, R., 1999. No association between the serotonin transporter promoter region (5-HTTLPR) and the dopamine D3 receptor (BalI D3DR) polymorphisms and heroin addiction. Mol. Psychiatry 4, 313–314.

Laer, S., Remmers, F., Scholz, H., Stein, B., Muller, F.U., Neumann, J., 1998. Receptor mechanisms involved in the 5-HT-induced inotropic action in the rat isolated atrium. Br. J. Pharmacol. 123, 1182–1188.

Lappalainen, J., Zhang, L., Dean, M., Oz, M., Ozaki, N., Yu, D.H., Virkkunen, M., Weight, F., Linnoila, M., Goldman, D., 1995. Identification, expression, and pharmacology of a Cys23–Ser23 substitution in the human 5-HT2C receptor gene (HTR2C). Genomics 27, 274–279.

Lappalainen, J., Long, J.C., Eggert, M., Ozaki, N., Robin, R.W., Brown, G.L., Naukkarinen, H., Virkkunen, M., Linnoila, M., Goldman, D., 1998. Linkage of antisocial alcoholism to the serotonin 5-HT1B receptor gene in 2 populations. Arch. Gen. Psychiatry 55, 989–994.

Lappalainen, J., Long, J.C., Virkkunen, M., Ozaki, N., Goldman, D., Linnoila, M., 1999. HTR2C Cys23Ser polymorphism in relation to CSF monoamine metabolite concentrations and DSM-III-R psychiatric diagnoses. Biol. Psychiatry 46, 821–826.

Lassig, J.P., Vachirasomtoon, K., Hartzell, K., Leventhal, M., Courchesne, E., Courchesne, R., Lord, C., Leventhal, B.L., Cook, E.H. Jr., 1999. Physical mapping of the serotonin 5-HT(7) receptor gene (HTR7) to chromosome 10 and pseudogene (HTR7P) to chromosome 12, and testing of linkage disequilibrium between HTR7 and autistic disorder. Am. J. Med. Genet. 88, 472–475.

Lenzinger, E., Neumeister, A., Praschak-Rieder, N., Fuchs, K., Gerhard, E., Willeit, M., Sieghart, W., Kasper, S.F., Hornik, K., Aschauer, H.N., 1999. Behavioral effects of tryptophan depletion in seasonal affective disorder associated with the serotonin transporter gene? Psychiatry Res. 85, 241–246.

Lerman, C., Caporaso, N.E., Audrain, J., Main, D., Boyd, N.R., Shields, P.G., 2000. Interacting effects of the serotonin transporter gene and neuroticism in smoking practices and nicotine dependencem. Mol. Psychiatry 5, 189–192.

Lesch, K.-P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Müller, C.R., Hamer, D.H., Murphy, D.L., 1996. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274, 1527–1531.

Li, Q., Wichems, C., Heils, A., Van De Kar, L.D., Lesch, K.P., Murphy, D.L., 1999. Reduction of 5-hydroxytryptamine (5-HT)(1A)-mediated temperature and neuroendocrine responses and 5-HT(1A) binding sites in 5-HT transporter knockout mice. J. Pharmacol. Exp. Ther. 291, 999–1007.

Lieberman, J.A., Safferman, A.Z., Pollack, S., Szymanski, S., Johns, C., Howard, A., Kronig, M., Bookstein, P., Kane, J.M., 1994. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. Am. J. Psychiatry 151, 1744–1752.

Linnoila, V.M., Virkkunen, M., 1992. Aggression, suicidality, and serotonin. J. Clin. Psychiatry 53, 46–51, Suppl.

Little, K.Y., McLaughlin, D.P., Zhang, L., Livermore, C.S., Dalack, G.W., McFinton, P.R., DelProposto, Z.S., Hill, E., Cassin, B.J., Watson, S.J., Cook, E.H., 1998. Cocaine, ethanol, and genotype effects on human midbrain serotonin transporter binding sites and mRNA levels. Am. J. Psychiatry 155, 207–213.

Lucas, J.J., Yamamoto, A., Scearce-Levie, K., Saudou, F., Hen, R., 1998. Absence of fenfluramine-induced anorexia and reduced c-Fos induction in the hypothalamus and central amygdaloid complex of serotonin 1B receptor knock-out mice. J. Neurosci. 18, 5537–5544.

Lucki, I., 1998. The spectrum of behaviors influenced by serotonin. Biol. Psychiatry 44, 151–162.

MacKenzie, A., Quinn, J., 1999. A serotonin transporter gene intron 2 polymorphic region, correlated with affective disorders, has allele-dependent differential enhancer-like properties in the mouse embryo. Proc. Natl. Acad. Sci. U. S. A. 96, 15251–15255.

Maestrini, E., Lai, C., Marlow, A., Matthews, N., Wallace, S., Bailey, A., Cook, E.H., Weeks, D.E., Monaco, A.P., 1999. Serotonin transporter (5-HTT) and gamma-aminobutyric acid receptor subunit beta3 (GABRB3) gene polymorphisms are not associated with autism in the IMGSA families. Am. J. Med. Genet. 88, 492–496.

Malhotra, A.K., Goldman, D., Ozaki, N., Rooney, W., Clifton, A., Buchanan, R.W., Breier, A., Pickar, D., 1996. Clozapine response and the 5HT2CCys23Ser polymorphism. NeuroReport 7, 2100–2102.

Malleret, G., Hen, R., Guillou, J.L., Segu, L., Buhot, M.C., 1999. 5-HT1B receptor knock-out mice exhibit increased exploratory activity and enhanced spatial memory performance in the Morris water maze. J. Neurosci. 19, 6157–6168.

Mann, J.J., Malone, K.M., Nielsen, D.A., Goldman, D., Erdos, J., Gelernter, J., 1997. Possible association of a polymorphism of the tryptophan hydroxylase gene with suicidal behavior in depressed patients. Am. J. Psychiatry 154, 1451–1453.

Mann, J.J., Huang, Y.Y., Underwood, M.D., Kassir, S.A., Oppenheim, S., Kelly, T.M., Dwork, A.J., Arango, V., 2000. A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. Arch. Gen. Psychiatry 57, 729–738.

Masellis, M., Basile, V., Meltzer, H.Y., Lieberman, J.A., Sevy, S., Macciardi, F.M., Cola, P., Howard, A., Badri, F., Nothen, M.M., Kalow, W., Kennedy, J.L., 1998. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology 19, 123–132.

Masellis, M., Basile, V.S., Ozdemir, V., Meltzer, H.Y., Macciardi, F.M., Kennedy, J.L., 2000. Pharmacogenetics of antipsychotic treatment: lessons learned from clozapine. Biol. Psychiatry 47, 252–266.

Mazzanti, C.M., Lappalainen, J., Long, J.C., Bengel, D., Naukkarinen, H., Eggert, M., Virkkunen, M., Linnoila, M., Goldman, D., 1998. Role of the serotonin transporter promoter polymorphism in anxiety-related traits. Arch. Gen. Psychiatry 55, 936–940.

McAskill, R., Mir, S., Taylor, D., 1998. Pindolol augmentation of antidepressant therapy. Br. J. Psychiatry 173, 203–208.

McDougle, C.J., Epperson, C.N., Price, L.H., Gelernter, J., 1998. Evidence for linkage disequilibrium between serotonin transporter protein gene (SLC6A4) and obsessive compulsive disorder. Mol. Psychiatry 3, 270–273.

Meltzer, H.Y., 1999. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology 21, 106S–115S.

Meltzer, H.Y., Matsubara, S., Lee, J.C., 1989. The ratios of serotonin2 and dopamine2 affinities differentiate atypical and typical antipsychotic drugs. Psychopharmacol. Bull. 25, 390–392.

Morabito, A., Gasperini, M., Macciardi, F., Smeraldi, E., 1982. Possible relationship between outcome in primary affective disorders treated with lithium and family history. Adv. Biochem. Psychopharmacol. 32, 157–163.

Mundo, E., Richter, M.A., Sam, F., Macciardi, F., Kennedy, J.L., 2000a. Is the 5-HT(1Dbeta) receptor gene implicated in the pathogenesis of obsessive-compulsive disorder? Am. J. Psychiatry 157, 1160–1161.

Mundo, E., Walker, M., Tims, H., Macciardi, F., Kennedy, J.L., 2000b. Lack of linkage disequilibrium between serotonin transporter protein gene (SLC6A4) and bipolar disorder. Am. J. Med. Genet. 96, 379–383.

Nagakura, Y., Akuzawa, S., Miyata, K., Kamato, T., Suzuki, T., Ito, H., Yamaguchi, T., 1999. Pharmacological properties of a novel gastrointestinal prokinetic benzamide selective for human 5-HT4 receptor vs. human 5-HT3 receptor. Pharmacol. Res. 39, 375–382.

Nakamura, T., Matsushita, S., Nishiguchi, N., Kimura, M., Yoshino, A., Higuchi, S., 1999. Association of a polymorphism of the 5HT2A receptor gene promoter region with alcohol dependence. Mol. Psychiatry 4, 85–88.

Nakhai, B., Nielsen, D., Linnoila, M., Goldman, D., 1995. Two naturally

occurring amino acid substitutions in the human 5HT1A receptor: 5HT1A-22 Gly–Ser and 5HT1A-28 Ile–Val. Biochem. Biophys. Res. Commun. 210, 530–536.

Nielsen, D., 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, D.A., Jenkins, G.L., Stefanisko, K.M., Jefferson, K.K., 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.

Nilsson, T., Longmore, J., Shaw, D., Olesen, I.J., Edvinsson, L., 1999. Contractile 5-HT1B receptors in human cerebral arteries: pharmacological characterization and localization with immunocytochemistry. Br. J. Pharmacol. 128, 1133–1140.

O'Reilly, R.L., Bogue, L., Singh, S.M., 1994. Pharmacogenetic response to antidepressants in a multicase family with affective disorder. Biol. Psychiatry 36, 467–471.

Osher, Y., Hamer, D., Benjamin, J., 2000. Association and linkage of anxiety-related traits with a functional polymorphism of the serotonin transporter gene regulatory region in israeli sibling pairs. Mol. Psychiatry 5, 216–219.

Ozaki, N., Rosenthal, N., Pesonen, U., Lappalainen, J., Felman-Naim, S., Schwartz, P., Turner, E., Goldman, D., 1996. Two naturally occurring amino acid substitutions of the 5-HT2A receptor: Similar prevalence in patients with seasonal affective disorder and controls. Biol. Psychiatry 40, 1267–1272.

Ozaki, N., Manji, H., Lubierman, V., Lu, S.J., Lappalainen, J., Rosenthal, N.E., Goldman, D., 1997. A naturally occurring amino acid substitution of the human serotonin 5-HT2A receptor influences amplitude and timing of intracellular calcium mobilization. J. Neurochem. 68, 2186–2193.

Pandey, S.C., Lumeng, L., Li, T.K., 1996. Serotonin2C receptors and serotonin2C receptor-mediated phosphoinositide hydrolysis in the brain of alcohol-preferring and alcohol-nonpreferring rats. Alcohol Clin. Exp. Res. 20, 1038–1042.

Parks, C.L., Robinson, P.S., Sibille, E., Shenk, T., Toth, M., 1998. Increased anxiety of mice lacking the serotonin1A receptor. Proc. Natl. Acad. Sci. U. S. A. 95, 10734–10739.

Peroutka, S.J., McCarthy, B.G., 1989. Sumatriptan (GR 43175) interacts selectively with 5-HT1B and 5-HT1D binding sites. Eur. J. Pharmacol. 163, 133–136.

Persico, A.M., Wang, Z.W., Black, D.W., Andreasen, N.C., Uhl, G.R., Crowe, R.R., 1995. Exclusion of close linkage between the synaptic vesicular monoamine transporter locus and schizophrenia spectrum disorders. Am. J. Med. Genet. 60, 563–565.

Persico, A.M., Militerni, R., Bravaccio, C., Schneider, C., Melmed, R., Conciatori, M., Damiani, V., Baldi, A., Keller, F., 2000. Lack of association between serotonin transporter gene promoter variants and autistic disorder in two ethnically distinct samples. Am. J. Med. Genet. 96, 123–127.

Pino, R., Cerbai, E., Calamai, G., Alajmo, F., Borgioli, A., Braconi, L., Cassai, M., Montesi, G.F., Mugelli, A., 1998. Effect of 5-HT4 receptor stimulation on the pacemaker current I(f) in human isolated atrial myocytes. Cardiovasc. Res. 40, 516–522.

Pritchard, J., Stephens, M., Rosenberg, N., Donnelly, P., 2000. Association mapping in structured populations. Am. J. Hum. Genet. 67, 170–181.

Ramboz, S., Oosting, R., Amara, D.A., Kung, H.F., Blier, P., Mendelsohn, M., Mann, J.J., Brunner, D., Hen, R., 1998. Serotonin receptor 1A knockout: An animal model of anxiety-related disorder. Proc. Natl. Acad. Sci. U. S. A. 95, 14476–14481.

Raymond, J.R., Mukhin, Y.V., Gettys, T.W., Garnovskaya, M.N., 1999. The recombinant 5-HT1A receptor: G protein coupling and signalling pathways. Br. J. Pharmacol. 127, 1751–1764.

Rietschel, M., Naber, D., Fimmers, R., Moller, H.J., Propping, P., Nothen, M.M., 1997. Efficacy and side-effects of clozapine not associated with variation in the 5-HT2C receptor. NeuroReport 8, 1999–2003.

Rioux, A., Fabre, V., Lesch, K.P., Moessner, R., Murphy, D.L., Lanfumey, L., Hamon, M., Martres, M.P., 1999. Adaptive changes of serotonin 5-HT2A receptors in mice lacking the serotonin transporter. Neurosci. Lett. 262, 113–116.

Rocha, B.A., Scearce-Levie, K., Lucas, J.J., Hiroi, N., Castanon, N., Crabbe, J.C., Nestler, E.J., Hen, R., 1998. Increased vulnerability to cocaine in mice lacking the serotonin-1B receptor. Nature 393, 175–178.

Rotondo, A., Nielsen, D.A., Nakhai, B., Hulihan-Giblin, B., Bolos, A., Goldman, D., 1997. Agonist-promoted down-regulation and functional desensitization in two naturally occurring variants of the human serotonin1A receptor. Neuropsychopharmacology 17, 18–26.

Rotondo, A., Schuebel, K., Bergen, A., Aragon, R., Virkkunen, M., Linnoila, M., Goldman, D., Nielsen, D., 1999. Identification of four variants in the tryptophan hydroxylase promoter and association to behavior. Mol. Psychiatry 4, 360–368.

Sabol, S.Z., Hu, S., Hamer, D., 1998. A functional polymorphism in the monoamine oxidase A gene promoter. Hum. Genet. 103, 273–279.

Samochowiec, J., Lesch, K.P., Rottmann, M., Smolka, M., Syagailo, Y.V., Okladnova, O., Rommelspacher, H., Winterer, G., Schmidt, L.G., Sander, T., 1999. Association of a regulatory polymorphism in the promoter region of the monoamine oxidase A gene with antisocial alcoholism. Psychiatry Res. 86, 67–72.

Sander, T., Harms, H., Lesch, K.P., Dufeu, P., Kuhn, S., Hoehe, M., Rommelspacher, H., Schmidt, L.G., 1997. Association analysis of a regulatory variation of the serotonin transporter gene with severe alcohol dependence. Alcohol Clin. Exp. Res. 21, 1356–1359.

Sander, T., Harms, H., Dufeu, P., Kuhn, S., Hoehe, M., Lesch, K.P., Rommelspacher, H., Schmidt, L.G., 1998. Serotonin transporter gene variants in alcohol-dependent subjects with dissocial personality disorder. Biol. Psychiatry 43, 908–912.

Sanger, G.J., 1996. 5-Hydroxytryptamine and functional bowel disorders. Neurogastroenterol. Motil. 8, 319–331.

Saudou, F., Amara, D., Dierich, A., LeMeur, M., Ramboz, S., Segu, L., Buhot, M.-C., Hen, R., 1994. Enhanced aggressive behavior in mice lacking 5-HT1B receptor. Science 265, 1875–1878.

Schuckit, M.A., Mazzanti, C., Smith, T.L., Ahmed, U., Radel, M., Iwata, N., Goldman, D., 1999. Selective genotyping for the role of 5-HT2A, 5-HT2C, and GABA alpha 6 receptors and the serotonin transporter in the level of response to alcohol: a pilot study. Biol. Psychiatry 45, 647–651.

Serretti, A., Lorenzi, C., Lilli, R., Smeraldi, E., 2000. Serotonin receptor 2A, 2C, 1A genes and response to lithium prophylaxis in mood disorders. J. Psychiatr. Res. 34, 89–98.

Shih, J.C., Ridd, M.J., Chen, K., Meehan, W.P., Kung, M.P., Seif, I., De Maeyer, E., 1999. Ketanserin and tetrabenazine abolish aggression in mice lacking monoamine oxidase A. Brain Res. 835, 104–112.

Sibille, E., Pavlides, C., Benke, D., Toth, M., 2000. Genetic inactivation of the Serotonin(1A) receptor in mice results in downregulation of major GABA(A) receptor alpha subunits, reduction of GABA(A) receptor binding, and benzodiazepine-resistant anxiety. J. Neurosci. 20, 2758–2765.

Smeraldi, E., Petroccione, A., Gasperini, M., Macciardi, F., Orsini, A., Kidd, K.K., 1984. Outcomes on lithium treatment as a tool for genetic studies in affective disorders. J. Affect. Disord. 6, 139–151.

Smeraldi, E., Zanardi, E., Benedetti, F., Di Bella, D., Perez, J., Catalano, M., 1998. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol. Psychiatry 3, 508–511.

Sodhi, M.S., Arranz, M.J., Curtis, D., Ball, D.M., Sham, P., Roberts, G.W., Price, J., Collier, D.A., Kerwin, R.W., 1995. Association between clozapine response and allelic variation in the 5-HT2C receptor gene. NeuroReport 7, 169–172.

Spielman, R., Ewens, W., 1996. The TDT and other family-based tests for linkage disequilibrium and association. Am. J. Hum. Genet. 59, 983–989.

Spielman, R.S., McGinnis, R.E., Ewens, W.J., 1993. Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). Am. J. Hum. Genet. 52, 506–516.

Spielman, R.S., Ewens, W.J., 1998. A sibship test for linkage in the presence of association: the sib transmission/disequilibrium test. Am. J. Hum. Genet. 62, 450–458.

Spurlock, G., Heils, A., Holmans, P., Williams, J., D'Souza, U.M., Cardno, A., Murphy, K.C., Jones, L., Buckland, P.R., McGuffin, P., Lesch, K.P., Owen, M.J., 1998. A family based association study of T102C polymorphism in 5HT2A and schizophrenia plus identification of new polymorphisms in the promoter. Mol. Psychiatry 3, 42–49.

Takahashi, N., Miner, L.L., Sora, I., Ujike, H., Revay, R.S., Kostic, V., Jackson-Lewis, V., Przedborski, S., Uhl, G.R., 1997. VMAT2 knockout mice: heterozygotes display reduced amphetamine-conditioned reward, enhanced amphetamine locomotion, and enhanced MPTP toxicity. Proc. Natl. Acad. Sci. U. S. A. 94, 9938–9943.

Tan, E.C., Yeo, B.K., Ho, B.K., Tay, A.H., Tan, C.H., 1999. Evidence for an association between heroin dependence and a VNTR polymorphism at the serotonin transporter locus. Mol. Psychiatry 4, 215–217.

Tecott, L., Sun, L., Akana, S., Strack, A., Lowenstein, D., Dallman, M., Julius, D., 1995. Eating disorder and epilepsy in mice lacking 5-HT2C serotonin receptors. Nature 374, 542–546.

Thomson, G., 1995. Mapping disease genes: family-based association studies. Am. J. Hum. Genet. 57, 487–498.

Tomkins, D.M., O'Neill, M.F., 2000. Effect of 5-HT(1B) receptor ligands on self-administration of ethanol in an operant procedure in rats. Pharmacol. Biochem. Behav. 66, 129–136.

Tordjman, S., Gutneckt, L., Carlier, M., Spitz, E., Antoine, C., Slama, F., Cohen, D.J., Ferrari, P., Roubertoux, P.L., Anderson, G.M., 2001. Role of the serotonin transporter in the behavioral expression of autism. Mol. Psychiatry, in press.

Travis, E.R., Wang, Y.M., Michael, D.J., Caron, M.G., Wightman, R.M., 2000. Differential quantal release of histamine and 5-hydroxytryptamine from mast cells of vesicular monoamine transporter 2 knockout mice. Proc. Natl. Acad. Sci. U. S. A. 97, 162–167.

Tsai, S.J., Hong, C.J., Wang, Y.C., 1999. Tryptophan hydroxylase gene polymorphism (A218C) and suicidal behaviors. NeuroReport 10, 3773–3775.

Turecki, G., Briere, R., Dewar, K., Antonetti, T., Lesage, A.D., Seguin, M., Chawky, N., Vanier, C., Alda, M., Joober, R., Benkelfat, C., Rouleau, G.A., 1999a. Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did or did not commit suicide. Am. J. Psychiatry 156, 1456–1458.

Turecki, G., Grof, P., Cavazzoni, P., Duffy, A., Grof, E., Ahrens, B., Berghofer, A., Muller-Oerlinghausen, B., Dvorakova, M., Libigerova, E., Vojtechovsky, M., Zvolsky, P., Joober, R., Nilsson, A., Prochazka, H., Licht, R.W., Rasmussen, N.A., Schou, M., Vestergaard, P., Holzinger, A., Schumann, C., Thau, K., Rouleau, G.A., Alda, M., 1999b. MAOA: association and linkage studies with lithium responsive bipolar disorder. Psychiatr. Genet. 9, 13–16.

Turker, T., Sodmann, R., Goebel, U., Jatzke, S., Knapp, M., Lesch, K.P., Schuster, R., Schutz, H., Weiler, G., Stober, G., 1998. High ethanol tolerance in young adults is associated with the low-activity variant of the promoter of the human serotonin transporter gene. Neurosci. Lett. 248, 147–150.

Uhl, G.R., 1999. Molecular genetics of substance abuse vulnerability: a current approach. Neuropsychopharmacology 20, 3–9.

Vickers, S.P., Clifton, P.G., Dourish, C.T., Tecott, L.H., 1999. Reduced satiating effect of d-fenfluramine in serotonin 5-HT(2C) receptor mutant mice. Psychopharmacology (Berl.) 143, 309–314.

Waldman, I.D., Robinson, B.F., Rowe, D.C., 1999. A logistic regression based extension of the TDT for continuous and categorical traits. Ann. Hum. Genet. 63, 329–340.

Wang, Y.M., Gainetdinov, R.R., Fumagalli, F., Xu, F., Jones, S.R., Bock, C.B., Miller, G.W., Wightman, R.M., Caron, M.G., 1997. Knockout of the vesicular monoamine transporter 2 gene results in neonatal death and supersensitivity to cocaine and amphetamine. Neuron 19, 1285–1296.

Whale, R., Quested, D.J., Laver, D., Harrison, P.J., Cowen, P.J., 2000. Serotonin transporter (5-HTT) promoter genotype may influence the prolactin response to clomipramine. Psychopharmacology (Berl.) 150, 120–122.

Yuan, X., Yamada, K., Ishiyama-Shigemoto, S., Koyama, W., Nonaka, K., 2000. Identification of polymorphic loci in the promoter region of the serotonin 5-HT2C receptor gene and their association with obesity and type II diabetes. Diabetologia 43, 373–376.

Zanardi, R., Benedetti, F., Di Bella, D., Catalano, M., Smeraldi, E., 2000. Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of the serotonin transporter gene. J. Clin. Psychopharmacol. 20, 105–107.