

## **2. GENETICS OF ANXIETY AND RELATED DISORDERS:**

### **Implications for Pharmacogenetics**

Klaus-Peter Lesch<sup>\*</sup>

#### **1. INTRODUCTION**

Treatment response to antidepressant, anxiolytic, and antipsychotic drugs is influenced by genetic factors and depends on the structure or functional expression of gene products. While treatment response is believed to involve both genetic and environmental factors, the contribution of an individual gene to drug response is likely to be modest. However, interactions between different genes may result in a dramatic modification of drug response (additive, nonadditive or multiplicative gene effects). The challenge faced by research into the genetic basis of psychopharmacological drug responses is to identify genes of relative small effect against a background of substantial genetic and environmental variation.

Emotionality, cognition, and motor functions as well as circadian and neuroendocrine rhythms including food intake, sleep and reproductive activity are both modulated by the brainstem raphe serotonin (5HT) system, and distinctively altered in anxiety spectrum and mood disorders. While 5HT controls a highly complex system of neural communication mediated by multiple pre- and postsynaptic 5HT receptor subtypes including the serotonin 1A receptor (5HT<sub>1A</sub>), high-affinity 5HT transport into the presynaptic neuron and thus maintenance of the 5HT pool available for subsequent release is

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K.P. Lesch, M.D., Molecular and Clinical Psychobiology, Department of Psychiatry and Psychotherapy, University of Wuerzburg, Fuechsleinstr. 15, 97080 Wuerzburg, Germany, E-mail: kplesch@mail.uni-wuerzburg.de

mediated by a unique protein (the 5HT transporter, 5HTT, SERT, SLC6A4), which is regarded as the initial sites of action of antidepressant/anxiolytics drugs and several potentially neurotoxic compounds, such as MDMA ("ecstasy"). Serotonergic antidepressants/anxiolytics, such as prototypical tricyclic clomipramine, and the selective 5HT uptake inhibitors (SSRIs), such as fluvoxamine, paroxetine, citalopram, and sertraline, occupy several pharmacologically distinct sites overlapping at least partially the substrate binding site. These agents are widely used in the treatment of depression, anxiety disorders, and impulse control disorders, as well as substance abuse including alcoholism.

Although several reviews have extensively discussed the general role of pharmacogenetics in individualising treatment of mood disorders with psychoactive compounds, pharmacogenetics implications of the treatment of anxiety spectrum disorders have not been addressed previously (Alda 2001; Catalano 1999; Lerer and Macciardi 2002; Mancama and Kerwin 2003; Serretti et al. 2002; Veenstra-VanderWeele et al. 2000). Therefore, the present chapter covers fundamental aspects of the genetics of anxiety-related traits, emotional responses, and anxiety disorders. The current status of conceptual issues in the search for candidate genes of human fearfulness and anxiety will also be considered. Finally, the evidence for a relationship between genetic variability of two serotonergic genes, 5HTT and 5HT<sub>1A</sub>, and response to antidepressant, anxiolytic, and antibipolar drugs as well as non-pharmacological treatments will be discussed.

## **2. GENETICS OF ANXIETY AND RELATED DISORDERS**

### **2.1. Anxiety-related traits in mood disorders**

A large body of evidence from family, twin, and adoptee studies has been accumulated that a complex genetic component is involved in anxiety-related traits and in the liability to anxiety spectrum disorders. While genetic research has typically focused either on normal personality characteristics or on psychiatric disorders, with few investigations evaluating the genetic and environmental relationship between the two, it is of critical importance to answer the questions whether a certain quantitative trait etiopathogenetically influences the disorder or whether the trait is a syndromal dimension of the disorder. Nevertheless, some studies have implicated anxiety-related personality traits, such as neuroticism or negative emotionality, in the comorbidity of mood disorders (Kendler et al. 1993a; Livesley et al. 1998). Separation of anxiety spectrum disorders from mood disorders including depression and bipolar disorder in current consensual diagnostic systems remarkably enhanced interest in the link between temperament, personality, and psychiatric disorders as well as the impact of this interrelationship on the heterogeneity within diagnostic entities, prediction of long-term course, and treatment response (Mulder et al. 1994). Based on multivariate genetic analyses of co-morbidity, generalized anxiety disorder and major depression have common genetic origins and the

phenotypic differences between anxiety and depression are dependent upon the environment (Kendler 1996; Kendler et al. 1992b). Moreover, indexed by the personality scale of neuroticism, general vulnerability overlaps genetically to a substantial extent with both anxiety and depression (Kendler et al. 1993a; b). These results predicted that when a quantitative trait locus (QTL), such as the 5HTT gene, is found for neuroticism, the same QTL should be associated with symptoms of anxiety and depression. Anxiety and mood disorders are therefore likely to represent the extreme end of variation in negative emotionality (Eley and Plomin 1997; Eley and Stevenson 1999). The genetic factor contributing to the extreme ends of dimensions of variation commonly recognized as an disorder may be quantitatively, not qualitatively, different from the rest of the distribution. This vista has important implications for identifying genes for complex traits related to a distinct disorders. Association of allelic variation of 5HTT function and mood disorders including unipolar depression and bipolar disorder has initially been reported by Collier and colleagues (1996) and subsequently by several other investigators, although some studies did not replicate these results (Lesch and Mössner 1998).

## **2.2. Generalized anxiety disorder**

Generalized anxiety disorder (GAD) is defined by excessive and uncontrollable worry about a number of life events or activities for least 6 month, accompanied by at least 3 of 6 associated symptoms of negative affect or tension, such as restlessness, fatigability, concentration difficulties, irritability, muscle tension, and sleep disturbance. Relative to other anxiety and mood disorders, GAD is more likely to show a gradual onset and/or life-long history of symptoms. While early ages of onset are common, the syndrome itself may emerge only later in life and a considerable number of patients with GAD report an onset in adulthood that is usually in response to psychosocial and emotional stress. Research has consistently shown that GAD is associated with high comorbidity rates for other psychiatric disorders, including panic disorder, major depression, dysthymia, social phobia, and specific phobia (Kendler et al. 1992a; Kendler et al. 1995a; Roy et al. 1995; Skre et al. 1994; Weissman 1993). Based on inadequate diagnostic reliability and high comorbidity the discriminant validity of GAD has been controversial. Studies have begun to address the structural relationship of the dimensions comprising various anxiety disorders and there is evidence that GAD-associated negative affect and worry are dispositional traits common to both anxiety and mood disorders. GAD may therefore be conceptualized as a trait dimension predisposing to other disorders and etiological models of GAD therefore integrate both psychosocial and biological factors. Twin and family-based studies indicate a clear genetic influence in GAD with a heritability of approximately 30%. GAD-associated genetic factors are completely shared with depression, while environmental determinants seem to be distinct (Kendler 1996; Kendler et al. 1992b). This notion is consistent with recent models of emotional disorders which view anxiety and mood disorders as sharing common vulnerabilities but differing on dimensions including, for instance, focus of attention or psychosocial liability.

### 2.3. Phobias

Phobias occur in several forms and specific phobias are linked to a particular object or situation. Social phobia as an example is an intense fear of becoming humiliated in a social setting or being painfully embarrassed in front of other people. Lifetime prevalence of social phobia was 9.5% in females and 4.9% in males, with about one-third being classified as individuals with generalized social phobia. Little is known about the psychobiology and heritability of specific phobias, although twin studies of common phobias and fears in unselected samples point toward a genetic influence (Stein 1998). Assessment of lifetime history of five unreasonable fears and phobias, including agoraphobia and social, situational, animal, and blood-injury phobia, in female twins resulted in heritabilities between 46% and 67% (Kendler et al. 1999). Correcting for unreliability of ascertainment, the liability to fears and their associated phobias is moderately heritable. Individual-specific environmental experiences play an important role in the development of phobias, while familial and other environmental factors appear to be of little etiological significance. Only few population-based association and linkage-disequilibrium studies have been conducted in phobias. Linkage-disequilibrium studies in a population capitalize on the likelihood that the susceptibility genes for a particular disorder probably came from one or a few founding members. Stein et al. (1998) excluded linkage between generalized social phobia and the genes of 5HTT and 5HT<sub>2A</sub> receptor, although modifier effects could not be ruled out. Interestingly, Furmark and coworkers (2004) reported a relationship between allelic variation of 5HTT function, amygdala excitability, and symptom severity in patients with social phobia. Individuals with one or two copies of the low-activity, short allele of the 5HTT promoter polymorphism exhibited significantly increased scores of anxiety-related traits, state anxiety, and enhanced right amygdala responsivity to anxiety provocation, compared with subjects homozygous for the high-activity variant.

### 2.4. Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) is a common, frequently chronic condition that occurs following life-threatening or horrific traumatic events. The lifetime incidence of PTSD in western societies is 10-15% and approximately 50% of individuals who have had an episode of PTSD develop chronic symptoms. Family and twin studies suggest a substantial genetic contribution to the pathogenesis of PTSD (Radant et al. 2001). However, PTSD is unique among psychiatric disorders since there is an explicit requirement for the presence of a precipitating environmental event. While some types of trauma exposure (e.g. natural disasters, assaults) are not influenced by individual characteristics, other types of trauma exposure may be associated with certain personality characteristics (e.g. engaging in high-risk activities) which are themselves under genetic influence.

Unfortunately, a quite broadly defined phenotype, specific requirement for an environmental exposure and high frequency of comorbid psychiatric illness

as well as genetic heterogeneity, incomplete penetrance, pleiotropy, and interaction multiple genes complicate genetic studies of PTSD and its treatment. One strategy to get around these problems is to perform genetic analysis of traits associated with PTSD, rather than PTSD itself, an approach that has yielded promising results for other diseases with complex genetics. Hypothalamic-pituitary-adrenal axis dysfunction, physiologic markers of increased arousal, and increased acoustic startle response are PTSD-associated traits accessible to genetic analysis. However, the power of these traits to distinguish PTSD from non-PTSD patients need to be determined before they can be employed in genetic studies. Only a few association studies have been reported. Comings et al. (1996) reported that the A1 allele of the dopamine D2 receptor gene (DRD2) was significantly more common among PTSD patients as compared to veteran controls. Differences in rates of substance abuse, which appear also be associated with the A1 allele may explain failure to replicate this finding (Gelernter et al. 1999). Similarly based on the assumption of an abnormal dopaminergic function in PTSD, Segman and associates (2002) examined the association of the dopamine transporter (DAT, SLC6A3) variable number tandem repeat (VNTR) polymorphism with PTSD. The study evaluated 102 chronic PTSD patients versus carefully-documented trauma survivors who did not develop PTSD. Significant excess of 9 repeat allele was observed among PTSD patients (43% vs 30.5% in TS controls) further supporting the notion that genetically influenced changes in dopaminergic reactivity may contribute to the occurrence of PTSD among trauma survivors. Finally, in a sample of male PTSD patients, dinucleotide repeat polymorphisms of the GABA<sub>A</sub> receptor  $\beta 3$  subunit gene (GABRB3) were associated with higher scores of somatic symptoms, anxiety, insomnia, social dysfunction, and depression (Feusner et al. 2001).

## 2.5. Panic disorder

Panic disorder (PD) is strikingly different from other types of anxiety in that panic attacks are sudden, appear to be unprovoked, and are often disabling. They may include intense fear, fear of dying or a sense that something unimaginably horrible is about to occur and one is powerless to prevent it or discomfort accompanied by several physiological symptoms, such as choking sensations, sweating, dizziness, fear of losing control or perceptual distortions. A panic attack typically lasts several minutes to hours and may be one of the most distressing experiences. Panic attacks are followed by persistent concerns about having additional attacks, worry about the implications of the attack or its consequences, and significant changes in behavior related to the attacks.

Following one or repeated panic attacks, patients may develop an irrational fear, or phobia, about these situations and begin to avoid them. At this stage, PD is complicated by agoraphobia. PD, agoraphobia, and depression display significant comorbidity. Familial patterns of aggregation also suggest that PD, GAD, depression, and agoraphobia may co-occur but it is still a matter of considerable debate whether they have related or different genetic etiologies (Maier et al. 1995; Weissman 1993; Woodman 1993). A higher correlation for

monozygotic twins (MZ) than for dizygotic twins (DZ) indicates genetic influences. Logistic regression analysis of PD family data yielded evidence of vertical transmission and the effect of sibship environment, whereas segregation analysis of family data resulted in moderate evidence of an incompletely penetrant dominant or recessive major gene (Bonney 1986; Hopper et al. 1990). Model fitting in a large twin sample found evidence that the familial transmission of panic-phobia was influenced by sex-dependent additive genetic effects, dominant genetic factors, individual-specific environmental factors, and a shared environmental effect for women only (16% vs 1%), while higher heritability in males (38%) compared to females (16%) was predicted (Kendler et al. 1995b).

Several genome-wide linkage scans for PD liability genes have been published. Although none of the findings based on lod scores or the proportion of allele sharing reached a level of statistical confidence according to stringent criteria, a region suggestive of a susceptibility locus for PD on chromosome 7p15 was independently identified in both studies. Crowe and associates (2001) detected the highest lod score of 2.23 at the D7S2846 locus, located at 57.8 cM on chromosome 7, in a region that lies within 15 cM from the D7S435 locus reported by Knowles et al. (1998). Linkage to numerous other markers over a substantial proportion of the human genome had previously been excluded under various parametric models in different sets of pedigrees (Crowe 1990; Crowe et al. 1990; Kato et al. 1996; Mutchler et al. 1990; Wang et al. 1992). Some of the conflicting results of linkage analyses in PD may be ascribed to methodological differences in family ascertainment, phenotype definition, diagnostic assessment, and approaches data analysis. Even more likely, they may represent true etiologic differences due to locus heterogeneity. Susceptibility to PD may thus be influenced either by an incompletely penetrant major gene in some families or by multiple genes of weak and varying effect in others.

Since evidence for a genetic liability in PD is persuasive, a small number of putative vulnerability genes have been assessed in association studies. A role of monoamine neurotransmitters in the etiology of PD has been suggested by the observations that increased serotonergic neurotransmission provokes anxiety even up to the level of panic attacks in PD patients. This corresponds well to the general observation that in rodent models increased serotonergic function is anxiogenic while a decrease is anxiolytic. Although it may be hypothesized that enhanced serotonergic neurotransmission in PD is due to decreased 5HT uptake, no association with allelic variation of 5HTT expression and PD was detected in different populations (Deckert et al. 1997; Hamilton et al. 1999; Ishiguro et al. 1997; Matsushita et al. 1997). These negative findings are compatible with the assumption that additional or alternative cellular pathways and neural circuits are involved in panic anxiety. Monoamine oxidase A (MAOA), an enzyme involved in the degradation of 5HT, dopamine, and norepinephrine and thus positioned at the crossroads of several monoaminergic system, is another plausible candidate gene. A 30-bp repeat polymorphism was identified in the promoter region of the MAOA gene that differentially modulates gene transcription (Deckert et al. 1999). Variation in the number of repeats of this

MAOA gene-linked polymorphic region (MAOALPR) displayed allele-dependent transcriptional efficiency. The effectiveness of the 3-repeat allele was 2-fold lower than those with longer repeats. Assessment of the MAOALPR for association with PD in two independent samples showed that the longer alleles were significantly more frequent in female patients than in females of the corresponding control populations (Deckert et al. 1999). Together with the observation that inhibition of MAOA is clinically effective in the treatment of panic disorder, particularly in women, these findings suggest that altered MAOA activity may be a gender-specific risk factor for PD. Recently, a functional single nucleotide polymorphism (SNP) in the transcriptional control region of 5HT<sub>1A</sub> (HTR1A-1019) was reported which displays differential binding efficiency of a repressors/enhancer-type transcriptional regulator (Lemondé et al. 2003). The G variant of this polymorphism was shown to be associated with anxiety- and depression-related personality traits as well as with the agoraphobic subtype of panic disorder (Rothe et al. 2004; Strobel et al. 2003). Finally, no consistently significant associations between PD and alleles of the GABA<sub>A</sub>, dopamine D2 and D4, cholecystokinin B as well as the adenosine A1 and A2a receptor genes have been detected (Crawford et al. 1995; Crowe et al. 1997; Deckert et al. 1998; Kato et al. 1996; Kennedy et al. 1999; Wang et al. 1998). Population-based studies also found no evidence for an association between PD and the gene for the DAT (Hamilton et al. 2000).

### 3. GENETIC VARIABILITY OF SEROTONIN TRANSPORTER FUNCTION

In humans, transcriptional activity of the 5HTT gene is modulated by a polymorphic repetitive element, 5HTT gene-linked polymorphic region (5HTTLPR) located upstream of the transcription start site. Comparison of different mammalian species confirmed the presence of the 5HTTLPR in simian primates but not in prosimian primates and other mammals (Lesch et al. 1997). The majority of alleles are composed of either 14 or 16-repeat units (short and long allele, respectively), while alleles with 15, 18-20, or 22 repeat copies, and most variants with single-base insertions/deletions or substitutions within individual repeats are rare. The distinctive structure of the 5HTTLPR gives rise to the formation of DNA secondary structure that has the potential to regulate the transcriptional activity of the associated 5HTT gene promoter. When fused to a luciferase reporter gene and transfected into human 5HTT expressing cell lines, the short (s) and long (l) 5HTTLPR variants differentially modulate transcriptional activity of the 5HTT gene and ultimately uptake function of the 5HTT protein (Lesch et al. 1996).

A growing body of evidence suggests a role of 5HTTLPR-dependent allelic variation in 5HTT expression and function in anxiety-, depression-, and aggression-related personality traits and syndromal dimensions of various psychiatric disorders (for review see Lesch 2003). The influence of genetically driven variability of 5HTT function on individual phenotypic differences in personality and behavior was explored in several independent population/family

genetic studies. The findings suggest that the 5HTTLPR influences traits of negative emotionality related to anxiety, depression, and stress responsiveness as well as aggressiveness. Nevertheless, several efforts to detect associations between the 5HTTLPR and personality traits have been complicated by the use of small sample sizes, heterogeneous subject populations, ethnic and sociocultural characteristics, and differing methods of personality assessment. In addition to the exploration of the impact of allelic variation in 5HTT expression on anxiety, depression, and aggression-related personality traits, a role of the low-activity s allele has been suggested in a variety of neuropsychiatric disorders (for review see Lesch 2003; Lesch and Mössner 1998).

Evidence for a modulatory effect of the 5HTTLPR on prefrontal cortex and amygdala activity suggests that genotype-phenotype correlations may be accessible to analysis of event-related potentials (ERP) or functional magnetic resonance imaging (fMRI) of the brain. In two subsequent studies, Fallgatter and associates (1999; 2004) reported an association between 5HTTLPR genotype and prefrontal cortex-limbic excitability detected with two different tasks of cognitive response control, Go-NoGo and error-processing task). Individuals with one or two s allele of the 5HTTLPR showed higher prefrontal brain activity as compared to subjects homozygous for the l variant, thus indicating that the 5HTTLPR s variant is linked to enhanced responsiveness of the prefrontal cortex, particularly the anterior cingulate cortex (ACC). These findings strongly suggest a relationship between cognitive brain function and allelic variation of 5HTT function. Hariri and coworkers (2002) reported that individuals with at least one copy of the 5HTTLPR s variant exhibit greater amygdala responsivity, as assessed by fMRI, in response to fearful stimuli compared with individuals homozygous for the high-activity l allele. This result confirms that genetically driven variation of serotonergic function contributes to the response of brain regions underlying human emotional behavior and indicate that differential excitability of the amygdala to emotional stimuli may contribute to increased fear and anxiety-related responses. The considerable effect sizes of both ERP and fMRI measures as well as their unique ability to assay information processing at the level of brain function during cognitive tasks in relatively small samples of individual and in the absence of noticeable behavioral differences, offers a powerful approach to functional genomics of the brain. The consistent results derived from these endophenotypic paradigms not only underscore the power of direct assessment of brain physiology in exploring the functional impact of genomic variation but also support the notion of a critical link between functional gene variation and differences in information processing within distinct neurocircuits that have been linked to the manifestation of distinct behavioral traits and behavioral disorders (Fallgatter et al. 2004).

#### **4. SEROTONIN TRANSPORTER AND ANTIDEPRESSANT/ANXIOLYTIC RESPONSE**

Based on theoretical consideration a complex interaction between genotype, behavioral or syndromal dimensions, and drug response has been predicted



(Catalano 1999). A given genetic predisposition, such as allelic variation in 5HTT function, may lead to both increased susceptibility to anxious or depressive features and less favorable antidepressant responses in patients affected by mood disorders. Impaired 5HTT function confers, if any, only a very modest susceptibility to depressed states, because adaptive mechanisms are likely to compensate for the deficiency, while more robust alterations of 5HT turnover observed during antidepressant treatment revealed robust effects of allelic variation of 5HTT function, 7-20% of variance of treatment effect) that lead to variable SSRI efficacy. Pharmacogenetic and other treatment response studies of the serotonin transporter gene are summarized in the following sections and in Table 1.

Smeraldi and associates (1998) investigated whether the 5HTTLPR genotype is related to the antidepressant response to the SSRI fluvoxamine and/or augmentation with the 5HT<sub>1A</sub> receptor antagonist pindolol in patients with major depression with psychotic features who had been randomly assigned to treatment with a fixed dose of fluvoxamine and either placebo or pindolol for 6 weeks. Both homozygotes for the l variant (l/l genotype) of the 5HTTLPR and heterozygotes (l/s) showed a better response to fluvoxamine than patients homozygous for the s variant (s/s). Interestingly, in the group treated with fluvoxamine plus pindolol all the genotypes acted like l/l treated with fluvoxamine alone and the genetic effect could not be detected. Thus, SSRI efficacy in delusional depression seems to be related, in part, to genetic variation of 5HTT function that in the subjects with s/s genotype pindolol may have compensated for the altered transcriptional activity of the 5HTT gene.

The effect of the 5HTTLPR genotype on antidepressant response was replicated in an independent sample of depressed patients treated with the SSRI paroxetine (Zanardi et al. 2000). In a study of elderly patients treated for depression, Pollock and associates (2000) found that patients with a l/l genotype displayed a faster response to paroxetine. The association appeared specific to paroxetine, as there was no genotypic difference with respect to the antidepressant response to nortriptyline, a predominantly noradrenergic drug. The same group also demonstrated an influence of the 5HTTLPR on platelet activation in geriatric depression (Whyte et al. 2001). More recently, Rausch and coworkers (2002) reported an association between the 5HTTLPR l/l genotype and improved response to fluoxetine and a placebo-controlled study confirmed a significant increase in response to the SSRI sertraline in elderly depressed patients homozygous for the l allele of 5HTTLPR compared with patients carrying one or two copies of the s variant. No significant difference was observed in the placebo group (Durham et al. 2003). Arias et al. (2003) confirmed the results of previous studies demonstrating a similar association between 5HTTLPR genotype and an therapeutic effect of the most selective SSRI citalopram. In patients with depression, the remission in the course of treatment was less likely in subjects with the s/s genotype.

**Table 1.** Pharmacogenetic and other treatment response studies of the serotonin transporter gene

Antidepressants/ Anxiolytics	Sample	Phenotype	Results
Smeraldi et al. 1998	Major depression (n=56) Major depression (n=46)	Response to fluvoxamine Response to fluvoxamine + pindolol	Better response in l/l and l/s subjects compared to s/s No difference in response to combination
Zanardi et al. 2000	Major depression (n=58)	Response to paroxetine	Better response in l/l and l/s subjects compared to s/s
Pollock et al. 2000	Major depression (n=95), elderly patients	Response to paroxetine or nortriptyline	More rapid response to paroxetine in l/l subjects, no effect on nortriptyline response
Kim et al. 2000	Major depression (n=120), controls (n=252), Koreans	Response to paroxetine or fluoxetine	Better response in s/s subjects, intron 2 VNTR also associated with response)
Yu et al. 2002	Major depression (n=121), Chinese	Response to fluoxetine	Better response in l/l subjects, l/l genotype less common
Yoshida et al. 2002	Major depression (n=66), Japanese	Response to fluvoxamine	Better response in s/s subjects, l/l genotype rare
Durham et al. 2003	Major depression (n=206), elderly patients, placebo-controlled	Response time to sertraline	Shortened response delay in l/l subjects at week 1 and 2 compared to l/s and s/s; no difference in placebo group
Perlis et al. 2003	Major depression (n=36)	Adverse effects of fluoxetine	Higher rate of insomnia and agitation in s/s subjects compared to l/s and l/l
Joyce et al. 2003	Major depression (n=169)	Response to fluoxetine or nortriptyline	Better response to both fluoxetine and nortriptyline in l/l and l/s subjects older than 25 years compared to s/s
Arias et al. 2003	Major depression (n=131)	Remission during citalopram	Higher rate of s/s in non-remission group compared to remission group

These findings may, however, apply primarily to European populations. Treatment of Korean and Japanese patient samples with fluoxetine, paroxetine, and fluvoxamine showed contradictory results as a better response was found in patients with a s/s genotype (Kim et al. 2000; Yoshida et al. 2002), whereas Yu and coworkers (2002) reported a superior response to fluoxetine in l/l in depressed patients from China. Possible explanations for these discrepancies are manifold. For example, allele frequencies of the 5HTTLPR 1 variant between European populations and both the Korean and the Japanese population differ significantly (54% vs. 25% and 26%). A low frequency of the l allele in both of these studies resulted in a small number of homozygous l/l patients. Furthermore, ethnic as well as environmental differences could also influence the genotypic response to SSRIs.

**Table 1 (continued):** Pharmacogenetic and other treatment response studies of the serotonin transporter gene.

Sleep deprivation/ light therapy	Sample	Phenotype	Results
Benedetti et al. 1999	Bipolar disorder, depressed (n=68)	Antidepressant effect of sleep deprivation	Better effect in l/l subjects compared to l/s and s/s
Benedetti et al. 2003	Bipolar disorder, depressed (n=22)	Antidepressant effect of light therapy combined with sleep deprivation	Effect more marked in l/l subjects compared to l/s and s/s
<b>Lithium</b>			
Del Zompo et al. 1999	Bipolar disorder (n=67), controls (n=103)	Response to lithium, 49 responders,  (18 nonresponders)	Higher frequency of l allele in nonresponders compared to controls
Serretti et al. 2001	Bipolar disorder (n=167),  unipolar depression (n=34)	Effect of prophylactic lithium treatment (episode frequency)	Fewer episodes before lithium treatment, but less reduction of episodes in s/s patients
<b>Switch, rapid cycling</b>			
Mundo et al. 2001	Bipolar disorder, antidepressant-induced mania, IM+ (n=27), bipolar disorder, IM- (n=29)	Presence/absence of mania (IM+/IM-) during antidepressant treatment	Increased frequency of s allele in IM+ compared to IM-; no effect of intron 2 VNTR
Rousseva et al. 2003	Bipolar disorder (n=305)	Lifetime history of antidepressant-induced mania/rapid cycling	Increased frequency of s allele in subjects with rapid cycling but not with antidepressant-induced mania
<b>Antipsychotics</b>			
Arranz et al. 2000	Schizophrenic disorder (n=200)	Response to clozapine	Higher rate of s/s in non-response group; five other primarily serotonergic genotypes contribute to the prediction of response
<b>5HT Challenge</b>			
Whale et al. 2000	Healthy females (n=7, l/l genotype), Healthy females, (n=7, s/s genotype)	Clomipramine-induced prolactin response	Higher response in l/l subjects
Reist et al. 2001	Male alcohol dependence (n=14), healthy (n=13)	Fenfluramine-induced prolactin response	Higher response in l/l subjects

Furthermore, an interaction between 5HTTLPR genotype and therapeutic efficacy of the antimanic/antibipolar agent lithium, which is assumed to act via serotonergic mechanisms, was demonstrated. Del Zompo and coworkers (1999)

reported a trend towards higher frequency of the l allele among lithium nonresponders compared to controls. Serretti et al. (2001) found an opposite result: the group homozygous for the s variant showed poorer response. However, this association appears to have been mainly due to a difference in pre-lithium frequency of episodes; there was no difference in episode frequency during lithium treatment.

Benedetti and coworkers (1998) reported that drug-free patients with bipolar depression who were homozygous for the l variant of 5HTTLPR show superior mood improvement after total sleep deprivation (TSD) than those with the s/l and s/s genotype. However, relapse following restoration of night sleep led to similar depression ratings in all genotype groups at the end of treatment. In a follow-up study the same group demonstrated that short-term relapse following acute response to TSD may be prevented by a combination of TSD with light therapy given during the TSD night and in the morning after recovery sleep and that the response is influenced by the 5HTTLPR with more marked effects in homozygotes for the l variant (Benedetti et al. 2003). These findings suggest that 5HTT function is critical for the antidepressant mechanism of action of sleep deprivation and light therapy, that presence of the l allele is associated with an increased reactivity of serotonergic system to a variety of stimuli, and support the notion that 5HTTLPR genotyping may represent a useful pharmacogenetic tool to individualize treatment of depression.

Finally, Mundo et al. (2001) found that 63% bipolar patients with a history of antidepressant-induced mania had the s allele compared to 29% in bipolar subjects who had been exposed to antidepressants, but did not develop mania. A role of the 5HTTLPR in rapid cycling, though not in antidepressant-induced mania, was supported in an independent cohort of patients with bipolar affective disorder, further supporting the notion that the low-activity s allele of the 5HTTLPR contributes to a pattern of affective instability (Rousseva et al. 2003). The role of allelic variation of 5HTT function in the development of adverse effects of SSRI treatment in patients with major depression was investigated by Perlis and coworkers (2003). A higher rate of fluoxetine-induced insomnia and agitation was found in s/s subjects compared to patients carrying the l/s and l/l genotypes. Although no antidepressant-induced mania was observed in this patient sample, these results seem plausible in the context of the findings that sleep disruption is a risk factor for the switch from depression to mania.

In addition to treatment response studies, 5HT system responsivity following pharmacologic challenge has been investigated with respect to genetic variability of the 5HTT function. Individuals with the l/l genotype exhibited greater prolactin response to either clomipramine or fenfluramine (Reist et al. 2001; Whale et al. 2000). Since the 5HTTLPR is likely to influence 5HT concentrations at all synapses, allelic variation in 5HTT function may affect the response to almost any agent affecting the 5HT system. This assumption would also explain an association between the s/s genotype and poor response to clozapine, an anxiolytically active antipsychotic displaying also a serotonergic mechanism of action (Arranz et al. 2000).

## 5. SEROTONIN 1A RECEPTOR AND ANTIDEPRESSANT/ANXIOLYTIC RESPONSE

While multiple lines of evidence implicate the serotonin 1A receptor (5HT<sub>1A</sub>) in the pathophysiology of anxiety and depression as well as in the mechanism of action of anxiolytics/antidepressants, its relevance to the therapeutic effectiveness of these drugs has been a matter of considerable debate (Griebel 1995; Hensler 2003; Hjorth et al. 2000; Lesch et al. 2003). The 5HT<sub>1A</sub> receptor is encoded by an intronless gene (*HTR1A*) located on human chromosome 5q12.3. Several rare missense polymorphisms, including the Gly22Ser variant which results in altered agonist-elicited downregulation, have been found within the protein coding of *HTR1A*. Moreover, Lemonde and coworkers (Lemonde et al. 2003) reported a functional C-1019G single nucleotide polymorphism (SNP) in the transcriptional control region of *HTR1A* (HTR1A-1019) and demonstrated in *in vitro* experiments that the G variant displays differential binding efficiency of the repressors/enhancer-type transcriptional regulator NUDR/DEAF-1. NUDR/DEAF-1 is co-expressed with both pre- and post-synaptic 5HT<sub>1A</sub> receptors, but its regulation of *HTR1A* transcription may differ in presynaptic raphe versus postsynaptic target cells (Lemonde et al. 2003).

Although initial association studies of the *HTR1A* variations produced ambiguous results in affective disorders (Arias et al. 2002; Nishiguchi et al. 2002), Lemonde and coworkers (2003) also showed that the G variant of the HTR1A-1019 polymorphism is associated with severe depression and suicidality. Taking the considerable comorbidity of depression and anxiety disorders into account it came as no surprise that associations of the G variant with anxiety- and depression-related personality traits, particularly with higher scores in Neuroticism and Harm Avoidance, as well as with the agoraphobic subtype of panic disorder were also reported (Rothe et al. 2004; Strobel et al. 2003). These findings have been further extended by Huang et al. (2004) who report an association of the HTR1A-1019 polymorphism with panic disorder as well as in schizophrenia and substance use disorder.

Preliminary evidence that allelic variation of 5HT<sub>1A</sub> receptor expression influences the response to antidepressant treatment has recently been provided by two independent studies. Serretti and colleagues (2004) assessed the severity of depressive symptoms in 151 patients with major depression and 111 bipolar patients before and following six weeks of treatment with the SSRI fluvoxamine and demonstrate that in bipolar disorder but not in unipolar depression, patients homozygous for the C variant of the HTR1A-1019 polymorphism showed a better response as compared to carriers of the G allele. Interestingly, the results failed to reveal an interaction between the HTR1A-1019 polymorphism and reported effects of the 5HTTLPR. Lemonde et al. (2004) reported that antidepressant response to the SSRI fluoxetine, noradrenaline reuptake inhibitor nefazodone, and 5HT<sub>1A</sub> agonist flibanserin, which desensitize the 5HT<sub>1A</sub> autoreceptor as one their mechanisms of action, was associated HTR1A-1019 polymorphism in 118 depressed patients. Patients homozygous for the G variant of the HTR1A-1019 polymorphism improved significantly less on flibanserin and

in pooled antidepressant treatment groups were twice as likely to be non-responders as those with the C/C genotype. These findings further corroborate the hypothesis that genetic variations in *HTR1A* may not only predispose to psychiatric disorders, but may also contribute to individual differences in responsiveness to antidepressant treatment.

Taken together, allelic variation in 5HT<sub>1A</sub> receptor expression seems to play a critical role in the development and modulation of individual differences in anxiety- and depression-related personality traits as well as in the pathophysiology of anxiety disorders and syndromal dimensions of depression, psychosis, and substance abuse. Evidence that the HTR1A-1019 polymorphism also influences therapeutic responses to serotonergic agents may have implications for tailoring individual antidepressant/anxiolytic treatment. The availability of an increasing number of functional gene variants within the serotonergic pathway together with integration of emerging concepts of developmental genetics of complex traits will provide the groundwork for the molecular dissection of syndromal dimensions and treatment response.

## 6. CONCLUSIONS

Response to psychopharmacologic drugs is genetically complex, results from an interplay of multiple genomic variations with environmental influences, and depends on the structure or functional expression of gene products, which are direct drug targets or are indirectly modify the development and synaptic plasticity of neural networks critically involved in their effects. During brain development, the 5HT system, which is commonly targeted by anxiolytic and antidepressant drugs, controls neuronal specification, differentiation, and phenotype maintenance. While formation and integration of these neural networks is dependent on the action of multiple proteins, converging lines of evidence indicate that genetically controlled variability in the expression of serotonergic genes is critical to the development and plasticity of distinct neurocircuits. The most promising finding to date indicate associations between the response time as well as overall response to serotonin reuptake inhibitors (SSRIs) and a common polymorphism within the transcriptional control region of both the 5HTT and 5HT<sub>1A</sub> genes. More functionally relevant polymorphisms in genes within a single neurotransmitter system, or in genes, which comprise a developmental and functional unit in their concerted actions, need to be identified and assessed in both large association studies to elucidate complex epistatic interactions of multiple loci. Finally, psychopharmacogenetic studies require to employ randomized, double-blind clinical trial methodology, and, in order to detect a small gene effects, a dimensional, quantitative approach to behavioral phenotypes and treatment effects arising from standardized psychometric trait and response assessment is needed. Given the limitation of the diagnostic and psychometric approach future studies will require extended, homogeneous, and ethnically matched samples.

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