Association between a Serotonin Transporter Length Polymorphism and Primary Insomnia

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Study Objective: To test the hypothesis that a 44-base-pair insertion/deletion polymorphism in the 5' regulatory region of the serotonin transporter gene (5-HTTLPR) is associated with primary insomnia.
Design: Association study.
Setting: Sleep laboratory at the Central Institute of Mental Health, Mannheim, Germany.
Patients: 157 patients with primary insomnia and 827 healthy controls.
Interventions: N/A.
Measurement and Results: We found the short (s-) allele of the 5-HTTLPR to be significantly more frequent in patients suffering from insomnia than in control individuals (47.1% vs. 39.9%: OR = 1.34).
Conclusions: This finding contributes to the understanding of the pathophysiology of primary insomnia and suggests a biological basis between the prevalent comorbidity of primary insomnia and other psychiatric disorders.
Keywords: Primary insomnia, polysomnography, 5-HTTLPR, serotonin, depression, genotype, susceptibility
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PRIMARY INSOMNIA, ACCORDING TO DSM-IV, IS ONE OF THE MOST FREQUENT SLEEP DISORDERS, WITH A PREVALENCE OF 3%[1,2] AND IS CHARACTERIZED BY difficulties initiating or maintaining sleep or nonrestorative sleep causing distress or impairment. The presence of learned, sleep-preventing associations, such as conditioned arousal to sleep-related cues and evidence for increased somatized tension are additional criteria for psychophysiological insomnia in the *International Classification of Sleep Disorders* (ICSD).

Large family and twin studies have consistently shown that insomnia is under strong genetic influence: first-degree relatives of patients with primary insomnia are at a 6.65-fold increased risk to develop insomnia themselves.[3,4] Among other factors, anxious-ruminative personality traits[5] and occurrence of stressful life events contribute to the onset and perpetuation of insomnia.[6] Thus, primary insomnia may be regarded as a potential consequence of gene-environment interaction.

Primary insomnia and other insomnia diagnoses show an association with mood disorders, with insomnia typically appearing before the onset of depression.[1] Therefore, insomnia could either be a risk factor for depression, or insomnia and affective disorders could share a common background, e.g., as a spectrum of stress-related disorders.

There is a longstanding discussion on the role of serotonin (5-HT) in the regulation of sleep.[7,8] In rodents and cats, it has been shown that typical, but not all[9] serotonergic raphe neurons discharge regularly during waking, at slower rates during slow wave sleep, and cease firing during paradoxical sleep,[10] which indicates serotonergic activity being related to wakefulness. In addition to this possible REM sleep inhibitory action, sleep facilitatory effects have also been reported,[11] likely due to the multitude of postsynaptic receptors, which mediate different responses. In particular, studies in humans support the $5HT_2$- receptor to be involved in slow wave sleep regulation.[12,13] Accordingly, several $5\text{-}HT_{2A}$ receptor antagonists or inverse agonists are currently being tested in randomized controlled trials for treatment of primary insomnia,[14] which underscores 5-HT's role in the regulation of sleep.

The key regulator of serotonin in the synapse, and therefore of overall serotonergic activity, is the 5-HT transporter (5-HTT). The presynaptic 5-HTT is the target of most antidepressants. A frequent variant of the 5-HTT gene (SLC6A4,17q11.2) is a 44 base-pair insertion/deletion polymorphism in the 5' regulatory region of the 5-HTT gene; and it affects gene transcription and transporter density in transfected cells. SLC6A4 genotype, usually grouped into "short" (s)- and "long" (l)-alleles, has been studied extensively with regard to psychiatric phenotypes and has been found to be associated with a variety of stress-related psychiatric conditions, such as trait anxiety[15,16] and risk for affective disorders,[17] especially in interaction with environmental adversity.[18,19] Moreover, the 5-HTTLPR s-allele has also been found associated with poor sleep quality in chronic stress[20] and worsened insomnia in depressed patients being treated with fluoxetine.[21] Based on these findings and on the role of psychosocial stress in pathophysiological concepts of primary insomnia,[22] we hypothesized that s-allele of 5-HTTLPR would be associated with primary insomnia.

METHODS AND MATERIALS

Primary Insomnia Patients

Our sleep laboratory is a referral center for patients with probable neuropsychiatric sleep disorders but not for patients with

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probable sleep-related breathing disorders. Between the years 2003 and 2007, we admitted 562 consecutive patients for polysomnography. One hundred fifty-seven patients with primary insomnia were drawn for this study (97 females, 60 males; age 45.7 ± 14.2 y), while 405 patients with other sleep-related diagnoses were excluded (obstructive sleep apnea syndrome n = 19). Patients with an apnea-hypopnea index (AHI) ≥ 10 and daytime sleepiness were excluded from the analyses. All diagnoses were performed within routine diagnostic purposes.

All 157 patients fulfilled the DSM-IV criteria of difficulty initiating or maintaining sleep, or nonrestorative sleep ≥ 6 months, as well as clinically significant distress or impairment due to the sleep disorder. The sleep disturbance did not occur exclusively during the course of other sleep and mental disorders and was not due to the direct physiological effects of a substance or a general medical condition. Additionally, in all patients we found positive evidence for increased tension as well as maladaptive behaviors, such as effortful attempts to fall asleep or maladaptive bedroom habits. To be included in the study, patients had to undergo a rigorous, multi-tiered phenotype characterization procedure. We only included patients who had a diagnosis of chronic primary insomnia and psychophysiological insomnia ≥ 6 months, according to DSM-IV and ICSD. Organic, substance-related, or psychiatric causes of insomnia were excluded by means of physical examination, ECG, and laboratory investigations. Since insomnia may not only be a risk factor for affective disorders, but is also a prevalent symptom in depressed patients in incomplete recovery, a semi-structured interview with a focus on current and lifetime affective disorder was done both at the pre-study outpatient visit and on admission for polysomnography. During the interview, all clinicians (M.D., M.S., C.S.) used the screening questions of the Structured Clinical Interview for DSM-IV (SCID) to screen psychiatric diagnoses; the presence of current or previous episodes of depression was controlled by checking all criteria of the syndrome. All patients were investigated by polysomnography for 2 consecutive nights. Nearly all patients meeting these inclusion criteria were included (refusal rate < 5%).

Based on family history, the majority of patients were Caucasians of German descent (n = 138) from the City of Mannheim and the Rhineland region. The remaining 19 patients were Caucasians of western European descent. Also, we identified 38 patients fulfilling the criteria of primary insomnia with previous episodes of major depression not being related to the current sleep disturbances.

Control Group

A total of 836 subjects from the Rhineland region (372 males, 455 females; age 54.6 ± 17.2 y) served as control group. They were randomly recruited from the list of registered inhabitants with the support of the local Census Bureau of the city of Bonn. All control subjects were of German descent. For the control group, the criterion "of German descent" was met when an individual's parents and 4 grandparents originated from Germany. All control individuals were screened for psychiatric disorders. This screening procedure can be summarized as follows: upon agreement to study participation, the volunteers were subjected to a thorough clinical assessment by an experienced psychiatrist or psychologist. Whenever this assessment hinted at a personal history of current or past psychiatric disorders, a structured SCID I interview was conducted. For the purpose of this study, only those control subjects with no psychiatric DSM-IV Axis I diagnosis (as captured by the SCID I: mood disorders, psychotic disorders, substance use disorders, anxiety disorders, eating disorders, and somatoform disorders) were included. This control group is identical to the control group studied by Hoefgen et al.[17] in an association study on major depressive disorder.

Informed Consent

Both patients and control group subjects gave written informed consent. The study protocol was approved by the Ethics Committees of the Universities of Heidelberg and Bonn.

Genotyping

Deoxyribonucleic acid (DNA) was isolated from whole blood by standard techniques. 5-HTTLPR variants were determined with polymerase chain reaction (PCR) techniques.

In the control group, oligonucleotide primers (forward: 5′-CCG CTC TGA ATG CCA GCA CC-3′, and reverse: 5′-CTG AGC TGG ACA ACC ACG GGC-3′) flanking the 5-HTT promoter polymorphic region were used to generate a 471-bp (deletion)/515-bp (insertion) fragment (Hoefgen). In the patient group, oligonucleotide primers (forward: 5′-GGC GTT GCC GCT CTG AAT GC-3′ and reverse: 5′-GAG GGA CTG AGC TGG ACA ACC AC-3′) generated a 484-bp (deletion)/528-bp (insertion) fragment.[16] PCR conditions were as described earlier.[16,17] Accuracy was assessed by duplicating 15% of the original sample, and reproducibility was 100%. In the patient group, 15 samples of each genotype were additionally genotyped with the control group primers. Results were 100% identical. Other genes were not analyzed.

Statistical Analysis

The distribution of genotype ("ll" vs. "ls" vs. "ss") and allele frequencies ("l" and "s" per population) were compared by a standard χ^2 test. Post hoc analyses were done with patient subgroups with German descent and without lifetime diagnoses of affective disorders, as well as separately in females and males. In the next step we controlled for the exclusion of patients with sleep apnea (AHI ≥ 10) in the group of patients, but not in the control group. In a hypothetical model, we excluded subjects of the control group, given the prevalence of sleep-disordered breathing (AHI ≥ 5) and self-reported hypersomnolence in large epidemiological samples (4%)[23] as well as using a conservative prevalence estimate of sleep apnea (10%). Genotype and allele frequency distribution of excluded control subjects in these models were used as reported earlier[24] (OR = 1.44 for l-allele). Results are presented as mean ± SD as appropriate.

RESULTS

For both patients and controls, genotype distributions were within Hardy-Weinberg expectations (1 *df* χ^2; P > 0.48). Genotyping failed in 1 patient (xl: n = 1).

The s-allele was significantly overrepresented in primary insomnia patients vs. controls (47.1% vs. 39.9%; χ^2 = 5.6, P = 0.018), conferring an odds ratio of 1.34 (95% CI: 1.05-1.71). On a genotypic level, the association was shy of nominal significance (P = 0.052) (Table 1). In order to retain power,

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we studied the complete, consecutively recruited sample of 157 patients (Table 1). When we included only the 138 patients of verified German descent, we observed a similar distribution of alleles and genotypes (allelic P-value = 0.019; genotypic P-value = 0.058).

We identified 38 patients with previous episodes of major depression, currently in full remission. After post hoc exclusion of these patients (remaining patients: 48 males/ 71 females; age: 45.4 ± 14.9 y), the finding still remained significant with the same distribution of s- and l-alleles (l: n = 121; s: n = 115; $\chi^2 = 6.8$, P = 0.012) and genotypes (ll: n = 29; sl: n = 63; ss: n = 26; $\chi^2 = 6.9$, P = 0.032).

In female subjects, the s-allele was significantly associated with primary insomnia at the level of allele distribution (50.7% vs. 41.2%; OR = 1.23; $\chi^2 = 4.5$, P = 0.0342) and showed borderline significance at the genotypic level ($\chi^2 = 5.0$, P = 0.0806). In male subjects, the OR (1.196) was similar, but the association was not significant either at the allelic (45.8% vs. 38.3%; $\chi^2 = 2.0$, P = 0.1551) or at the genotype level ($\chi^2 = 3.2$, P = 0.1986).

Post hoc exclusion of 4% of the control group in order to model the exclusion of sleep apnea led to minimal changes of the model, with the s-allele still being significantly overrepresented in patients with primary insomnia compared to controls (47.1% vs. 40.2%, $\chi^2 = 5.1$, P = 0.024), conferring an odds ratio of 1.32 (95% CI: 1.04-1.69). Using a conservative estimate of 10% of patients with sleep apnea using the assumed allelic distribution in sleep apnea,[24] we still found the s-allele to be significantly related to primary insomnia compared to controls (47.1% vs. 40.8%, $\chi^2 = 4.3$, P = 0.039), with an odds ratio of 1.30 (95% CI: 1.01-1.66).

The 5-HTTLPR was not associated with polysomnographic measures of sleep disturbance (Table 2), suggesting an association with the manifestation, but not the severity of insomnia.

Table 1—Allele and genotype distribution of the 5-HTLPPR (absolute numbers and frequencies) in patients with insomnia and healthy controls

	genotypes			alleles	
	ll	sl	ss	l	s
healthy controls* (n = 827)	294 (35.5%)	406 (49.1%)	127 (15.4%)	994 (60.1%)	660 (39.9%)
primary insomnia patients** (n = 157)	41 (26.3%)	83 (53.2%)	32 (20.5%)	165 (52.9%)	147 (47.1%)

**genotyping failed in 1 individual.

Table 2—Sleep efficiency and latency, sleep stages and genotype distribution in patients with primary insomnia

	genotypes*			ANOVA	
	ll (n = 19)	sl (n = 45)	ss (n = 19)	*F*	P
sleep efficiency (%)	78.7 ± 8.8	76.1 ± 13.6	79.0 ± 11.6	0.52	0.595
total sleep time (min)	371.6 ± 40.31	355.1 ± 69.4	362.4 ± 57.0	0.50	0.609
sleep latency (min)	22.5 ± 22.1	26.4 ± 17.8	20.7 ± 24.7	0.60	0.549
wake periods (number)	35.6 ± 18.1	34.2 ± 18.5	36.5 ± 17.5	0.12	0.889
wake (%)	16.3 ± 8.7	17.8 ± 12.7	15.7 ± 11.4	0.26	0.771
S1 (%)	11.7 ± 6.8	13.7 ± 8.1	13.3 ± 11.2	0.34	0.710
S2 (%)	50.4 ± 9.6	48.5 ± 14.0	50.4 ± 12.3	0.23	0.796
SWS (%)	6.1 ± 8.6	5.1 ± 5.8	5.3 ± 7.1	0.16	0.851
REM (%)	15.4 ± 4.0	14.8 ± 6.0	15.2 ± 6.8	0.07	0.929
arousal index	5.7 ± 5.3	8.0 ± 6.8	7.1 ± 6.5	0.83	0.441

*Patients with lifetime affective disorders and patients using hypnotic medication were not included in the analysis.

DISCUSSION

In a carefully characterized Caucasian sample, we report the first data showing an association between the 5-HTTLPR s-allele genotype and primary insomnia, implicating genotype-related neuronal processing in the genetic susceptibility architecture of primary insomnia.

Our findings were robust when potentially confounding conditions were excluded in post hoc analyses. In particular, neither the exclusion of patients with non-German descent nor the exclusion of patients with a lifetime diagnosis of affective disorders changed our finding. Moreover, by design, insomnia and other sleep disorders were not specifically excluded in the control group, meaning that testing against controls in which primary insomnia were excluded could have revealed an even larger effect of SLC76A4 genotype.

The limited number of subjects in our group of patients with primary insomnia may be considered a limitation of our study. Also, our group of patients with primary insomnia included a number of patients with lifetime affective disorders. Since the exclusion of current psychiatric disorders is key in the diagnosis of primary insomnia, a thorough psychiatric interview identified all patients with lifetime affective disorders. We preferred to compare patients with primary insomnia with a population-based sample instead of patients with other sleep disorders, since features of insomnia are difficult to differentiate in patients with restless legs syndrome, periodic limb movement disorder, or parasomnias.

Also, our procedures have excluded all patients with other sleep disorders, including a limited number of patients with sleep apnea, known to be related to l-allele of the 5-HTTLPR.[24] Epidemiological data indicate 2% of female and 4% of male middle-aged subjects suffer from sleep disordered breathing (AHI ≥ 5) and self-reported hypersomnolence,[23] which is a lower threshold than used for exclusion of our group of patients due to sleep apnea. However, the definitional exclusion of subjects with sleep apnea from the primary insomnia group could conceivably have led to an ascertainment bias. Therefore, we modeled the exclusion of subjects with sleep apnea from the control group using these prevalence rates, which did not appreciably change the association of the s-allele with primary insomnia. This is compatible with the literature, as the l-allele was reported to be sig-

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nificantly related to sleep apnea in male, but not female patients, and a sex-dependent effect was supposed.[24] Thus, our finding of an association between the s-allele of 5-HTTLPR with primary insomnia in female subjects is in our view not likely due to selective exclusion of sleep apnea in our group of patients. By definition of primary insomnia, other potential causes of disturbed sleep have to be excluded. Therefore, we consider the exclusion of patients with sleep apnea not to induce a selection bias, but rather to restrict the phenotype of primary insomnia in our group of patients. Of course, the fact that sleep disorders were not specifically excluded in the control group not only led to a potential underestimation of the effect of the SLC76A4 genotype being associated with insomnia, but also to a selective removal of subjects with sleep apnea in the patient group, being a potential confound with regard to the l genotype.

Thus, our data show a robust association between 5-HTTLPR and primary insomnia. Since this was also found in subjects without any lifetime affective disorders, our data indicate that this polymorphism is independently associated with both, insomnia and depression, and may be considered a risk factor contributing to both disorders. These new genetic data suggest that the association of insomnia with subsequent depression may not only reflect, as commonly assumed,[25] a life event contributing to depression as a stressor, but may have a common biological background as two conditions of a spectrum of stress-related disorders.

Since the 5-HTTLPR has been found associated with processing style for negative information[26] and emotion,[27] these mechanisms may generally predispose to disorders, in which learned associations play a role, like primary insomnia, social phobia[28] and depression.[17-19] In particular, carriers of the short variant of 5-HTTLPR show a functional uncoupling in brain circuits between perigenual cingulate and amygdala considered to be relevant to the extinction of negative affect.[27] Thus, carriers of the s-allele of the 5-HTTLPR may be predisposed to classical conditioning of sleeplessness with situational, temporal, or behavioral stimuli normally associated with sleep. Moreover, 5-HTTLPR is associated with the reactivity of the hypothalamus-pituitary-adrenal (HPA) system.[29] Therefore, it seems possible that 5-HTTLPR in the presence of stress contributes to increased evening HPA system activity, which is related to nocturnal awakening in healthy subjects as well as in patients with primary insomnia.[30] As life stress has been shown to interact with the 5-HTTLPR genotype, leading to increased amygdala activity even at rest,[31] s-allele carriers may be at risk for chronic hyperarousal in the context of recent adversity, a typical symptom of psychophysiological insomnia. Thus, 5-HTTLPR may contribute to the aspects of learned sleep-preventing associations as well as increased tension, hyperarousal and activation of stress-responsive systems, which may lead to primary insomnia. Moreover, based on this convergence with mechanisms for affect regulation and anxiety, we hypothesize that the association of primary insomnia with affective and anxiety disorders[32] may be partly mediated through a common genetic background.

Therefore, 5-HTTLPR should be regarded less as simply causing primary insomnia. Rather 5-HTTLPR may predispose the individual to stress-related reactions in the context of a stressful life event, such as conditioned arousal, HPA system activation, or hypervigilance. In our patients, we did not only confirm sleep disturbance by polysomnography and exclude other causes of the sleep disorder according to the DSM concept of primary insomnia. Moreover, in line with the ICSD concept of psychophysiological insomnia, these patients showed a pattern of increased tension and maladaptive behavior. Similar to the stressor-genotype interaction being described for depression,[18] carriers of the s-allele of 5-HTTLPR may be at risk for conditioned disturbed sleep in the context of stressful events being assumed to play a role in the pathogenesis of psychophysiological insomnia. The mechanisms may be similar in a wide array of stress-related disorders ranging from insomnia to anxiety and affective disorders.

Because insomnia is a common condition that leads patients in primary care, awareness and diagnosis of primary insomnia may identify a population at risk for depression. As the common sequence insomnia-depression may not only be explained by unspecific stress, but also common genetic factors, treating insomnia only may not necessarily lead to a substantial risk reduction with regard to depression.

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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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