A single nucleotide polymorphism in the HOMER1 gene is associated with sleep latency and theta power in sleep electroencephalogram

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Running Head: HOMER1 polymorphism, sleep latency and theta power.

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Abstract

Glutamate is the most excitatory neurotransmitter in the central nervous system and it is involved in the initiation and maintaining of waking and rapid-eye-movement (REM) sleep. Homer proteins act in the trafficking and/or clustering of metabotropic glutamate receptors, and polymorphisms in the HOMER1 gene have been associated with phenotypes related to glutamate signaling dysregulation. In this study, we report the association of a single nucleotide polymorphism (SNP) in the HOMER1 gene (rs3822568) with specific aspects of sleep in a sample of the Brazilian population. To accomplish this, 1,042 individuals were subjected to a full-night polysomnography, and a subset of 983 subjects had rs3822568 genotyping data available. When compared with the A allele carriers, GG genotyped individuals showed higher sleep latency, lower sleep efficiency, reduced number of arousals per hour, lower apnea-hypopnea index (AHI) and lower theta spectral power. In summary, the present findings suggest that the rs3822568 polymorphism in the HOMER1 gene is associated with sleep EEG profiles and might have an impact on sleep quality and sleep structure, with potential to explain inter-individual variation in sleep homeostasis.

Keywords: Genetic epidemiology, rs3822568, Sleep disorders, Sleep homeostasis, SNP, HOMER gene.
INTRODUCTION

The sleep-wake cycle depends on a complex and well-orchestrated neuronal circuitry involving diverse neurotransmitter signaling that induce and maintain sleep and wakefulness. Glutamate, the most excitatory neurotransmitter in the central nervous system, shows dynamic changes in its levels throughout the sleep-wake states (1). In addition, it is involved in the initiation and maintaining of waking and rapid eye movement (REM) sleep (2). The function of glutamate as a signaling molecule in the brain is accomplished by its multiple receptor subtypes working through selective intracellular targeting mechanisms (3).

The Homer protein family has been implicated in the trafficking and/or clustering of metabotropic glutamate receptors, playing roles on critical glutamatergic signaling pathways (4). These proteins are encoded by three different genes – Homer1, Homer2 and Homer3 – predominantly expressed at the nervous system as several isoforms resulting from alternative splicing events (5). Among the splicing variants, Homer1a is a non-constitutive short form, induced under high neuronal activity associated with decreasing glutamate signaling (6), identified as the most specific transcriptional marker for sleep loss (7). It was already been observed an increase in the expression of this transcript variant induced by sleep deprivation; it has been proposed that its up regulation modulates the increased neuronal glutamatergic activity found in prolonged wakefulness (7).

Single nucleotide polymorphisms (SNPs) – genomic loci where two or more alleles differ at a single base – have been associated with complex phenotypes, providing important molecular markers and unraveling risk loci for disease susceptibility (e.g. 8,9). Polymorphisms in the HOMER1 gene have been associated with disorders and traits related to glutamate signaling dysregulation, such as schizophrenia and cocaine dependence (10-12). We hypothesize that, given the importance of the glutamatergic system regulating sleep and prolonged wakefulness, genetic variation in the HOMER1 gene might explain inter-individual variability in several sleep traits measured using polysomnography. The goal of the present study was to evaluate the association of a specific SNP in the HOMER1 gene with specific aspects of sleep in a representative sample of the Brazilian population.
MATERIAL AND METHODS

Subjects

Subjects consisted of a sample of 1,042 individuals from the São Paulo Epidemiological Sleep Study (EPISONO), a population-based survey to represent São Paulo city population, delineating the epidemiological profile of sleep disorders in a metropolitan Brazilian city according to gender, age, and socioeconomic status in 2007. All individuals answered questionnaires about socioeconomic, demographic, lifestyle and general health factors. Blood samples were collected to investigate genetic traits and polysomnographic recordings were taken to access objective sleep quality. This study was approved by the Ethics Committee of the Federal University of São Paulo (CEP 0593/06) and was registered under ClinicalTrials.gov (NCT00596713; Epidemiology of sleep disturbances among adult population of the São Paulo City). All participants signed up informed consent forms.

Polysomnography and Clinical Assessment

A full-night polysomnography was performed using a digital system (EMBLA® S7000, Embla Systems, Inc., Broomfield, CO, USA) at the sleep laboratory. Physiological variables were monitored continuously, and recordings were scored according to standardized criteria (13,14). Obstructive sleep apnea syndrome (OSAS) was considered positive if individuals had an apnea-hypopnea index (AHI) between 5 and 14.9 and presented at least one of the following complaints: loud snoring, daytime sleepiness, fatigue, and breathing interruptions during sleep. Subjects with an AHI \(\geq 15\) were also considered positive, regardless whether they presented complaints (15).

Spectral Analysis of Sleep EEG

A specific syntax in R (version 2.10.1) was used for the spectral analysis of the sleep electroencephalography (EEG), performed according to previously published studies (16,17). Briefly describing, waves from C3-A2, C4-A1, O1-A2, and O2-A1 derivations were decomposed into delta (<4 Hz), theta (4–7.9 Hz), alpha 1 (8–9.9 Hz), alpha 2 (10–12.9 Hz), beta 1 (13–17.9 Hz), beta 2 (18–29.9 Hz), and gamma (\(\geq 30\) Hz) frequency bands using fast Fourier transformation, with a sampling rate of 200 Hz,
using epochs of 20 seconds. The filter settings used were in accordance to standard criteria of sleep EEG data acquisition (low frequency filter = 0.3 Hz; high frequency filter = 35 Hz; time constant = 0.3 seconds; and notch filter = 60 Hz). Artifact removal was performed as previously described (16).

### rs3822568 Genotyping

Genomic DNA was extracted from the volunteers’ white blood cells through the salting out of the cellular proteins and precipitation with a saturated NaCl solution (18). HOMER1 SNP rs3822568 was amplified by PCR (Polymerase Chain Reaction) using the primers H1F: 5’CCTGTTCACTGAGAAGAGCCTA3’ and H1R: 3’GAAATACAGCAGCCCGTCAT5’, under the following thermal conditions: 5 min at 95°C; 35 cycles of 0.5 min at 95°C, 0.5 min at 66°C, and 0.5 min at 72°C; 5 min at 72°C; held at 4°C. The 25 µl PCR mixes included 2.5 µl 10X PCR buffer, 0.75 µl MgCl₂ (1.5 mM), 0.5 µl of each primer, 0.5 µl of dNTP mix (2mM dATP, 2mM dCTP, 2mMdTTP, and 2mM dGTP), 0.25 µl of Taq DNA Polymerase, and 1.0 µl of DNA template (100ng/µl). Due to the presence of restriction sites inside the HOMER1 sequence, genotypes were determined using the Restriction Fragment Length Polymorphism (RFLP) method. Restriction endonuclease digestions were carried out directly on PCR products in 20 µl reactions containing 0.2 µl 10X buffer solution, 0.25 µl PvuII (New England Biolabs), and 5.0 µl PCR product. The PvuII enzyme cleaves the palindromic sequence CAG^CTG, providing a three-band profile (397pb, 218pb, and 178pb) for subjects carrying the A/G genotype; a two-band profile (218pb and 178pb) for homozygous A/A; and the single-band profile (397pb) for homozygous G/G. Digestion took place at 37°C for 16 hours, and the obtained profiles were visualized in 1% agarose gels, stained with ethidium bromide.

### Statistical analysis

The chi-square test was used to verify whether HOMER1 genotype frequencies were distributed according to the Hardy-Weinberg Equilibrium. One-way Analysis of Variance (ANOVA) followed by Bonferroni post hoc test was used to verify the effect of HOMER1 polymorphism on the z-score standardized polysomnographic parameters and sleep EEG spectral data. Also, the chi-square test was performed to compare genotype frequencies between individuals with and without OSAS. Furthermore, a set of 31
ancestry informative markers was used to estimate the genetic ancestry proportions of the population as previously described (19). General linear models (GLM) were applied to verify the effect of potential confounders (age, sex, body mass index and ancestry proportions) on the genetic association results of the continuous variables. Tests were performed using PAWS 18.0 (SPSS, Inc.), with a significance level of 0.05. Results are represented as mean [standard deviation].

RESULTS

A total of 983 individuals (42.43 [14.36] years; 55.8% females) had valid genotypes for the HOMER1 polymorphism rs3822568. Genotype frequencies for this SNP were 219 (22.3%), 469 (47.7%) and 295 (30.0%) for AA, AG and GG, respectively, and genotype distribution did not show deviations from Hardy-Weinberg Equilibrium ($\chi^2=1.58; p=0.209$).

We verified the association of HOMER1 rs3822568 genotypes with a number of polysomnographic parameters, as show in Table 1. We found significant associations between rs3822568 and sleep latency ($F_{(2,980)}=6.389, p=0.002$), sleep efficiency ($F_{(2,980)}=2.962, p=0.033$), number of arousals per hour ($F_{(2,980)}=6.075, p=0.002$) and apnea-hypopnea index ($F_{(2,980)}=3.988, p=0.019$). In summary, GG genotype carriers showed higher sleep latency in minutes (20.48 [29.74]) than AG genotype carriers (14.57 [16.23], Bonferroni post hoc $p=0.001$) and lower sleep efficiency (80.56 [13.95]) than AG genotype carriers (82.94 [11.71], Bonferroni post hoc $p=0.040$). In addition, GG carriers showed lower arousals per hour index (13.27 [9.12]) and AHI (6.63 [11.13]) than AA genotype carriers (16.61 [11.6]; Bonferroni post hoc $p=0.002$; and 9.89 [14.98]; Bonferroni post hoc $p=0.016$, respectively). We also found a trend for association between HOMER1 rs3822568 polymorphism and the percentage of stages N3, but no significant associations were found after the post hoc test (Table 1). Also, despite the association between this SNP and the apnea-hypopnea index levels, no significant association with the presence of OSAS was found ($\chi^2=4.104; p=0.128$).
Table 1- Sleep parameters measured by polysomnography comparing the three *HOMER1* rs3822568 SNP genotypes.

<table>
<thead>
<tr>
<th>Polysomnographic parameter</th>
<th>rs3822568 genotype</th>
<th>N</th>
<th>Mean (SD)</th>
<th>F(2,980)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency (minutes)</td>
<td>AA</td>
<td>219</td>
<td>17.14 (21.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>14.57 (16.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>20.48 (29.74) *</td>
<td>6.389</td>
<td>0.002</td>
</tr>
<tr>
<td>REM sleep latency (minutes)</td>
<td>AA</td>
<td>219</td>
<td>98.71 (54.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>102.03 (54.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>98.01 (52.22)</td>
<td>0.596</td>
<td>0.551</td>
</tr>
<tr>
<td>Sleep total time (minutes)</td>
<td>AA</td>
<td>219</td>
<td>346.19 (85.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>347.28 (71.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>333.82 (80.64)</td>
<td>2.962</td>
<td>0.052</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>AA</td>
<td>219</td>
<td>81.18 (13.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>82.94 (11.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>80.56 (13.95) *</td>
<td>3.433</td>
<td>0.033</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>AA</td>
<td>219</td>
<td>4.86 (3.72)</td>
<td>1.725</td>
<td>0.179</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>4.68 (3.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>4.33 (3.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>AA</td>
<td>219</td>
<td>54.87 (8.75)</td>
<td>0.284</td>
<td>0.753</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>54.67 (9.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>54.28 (9.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stages N3 (%)</td>
<td>AA</td>
<td>219</td>
<td>21.23 (7.35)</td>
<td>3.276</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>21.53 (8.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>22.85 (8.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>AA</td>
<td>219</td>
<td>19.04 (6.72)</td>
<td>0.771</td>
<td>0.463</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>19.13 (6.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>18.54 (6.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awake time (minutes)</td>
<td>AA</td>
<td>219</td>
<td>62.72 (50.2)</td>
<td>0.868</td>
<td>0.420</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>57.83 (44.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>59.74 (43.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of arousals per hour</td>
<td>AA</td>
<td>219</td>
<td>16.61 (11.6)</td>
<td>6.075</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>15.16 (11.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>13.27 (9.12) *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
<td>AA</td>
<td>219</td>
<td>9.89 (14.98)</td>
<td>3.988</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>469</td>
<td>8.33 (13.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>295</td>
<td>6.63 (11.13) *</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One-way ANOVA on z-score standardized measurements; SD: standard deviation; REM: rapid eye-movement.

* Indicates p<0.05 when compared to the other genotypes inside each variable.

To verify the effect of potential confounders on the identified associations, we fitted GLMs using *HOMER1* rs3822568 genotypes as well as sex, age, BMI and European ancestry proportion derived from ancestry informative markers as independent variables and the z-score of each significantly associated...
parameter in univariate analyses as dependent variables in each model. After adjustment for the studied confounders, \textit{HOMER1} rs3822568 polymorphism was significantly and independently associated only with sleep latency, regardless of other variables in the model (p=0.005).

Comparing the spectral power of each studied bandwidth in each sleep stage for each EEG derivation, we found significant associations between \textit{HOMER1} rs3822568 polymorphism and theta spectral power in all EEG derivations, even after adjustment for sex, age, BMI and European ancestry proportion. Overall, GG genotype carriers showed lower theta spectral power in stage 1, stage 2 and REM sleep; however, after adjustment for potential confounders, associations remained significant only in the occipital derivations and in sleep stage 1 and REM sleep (Table 2). No significant associations with other bandwidths were found.
Table 2: Significant associations between *HOMER1* rs3822568 polymorphism genotypes and theta (4–7.9 Hz) spectral power in sleep electroencephalogram. Results are shown by derivation and sleep stage.

<table>
<thead>
<tr>
<th>Derivation</th>
<th>Sleep Stage</th>
<th>rs3822568 Genotype</th>
<th>df</th>
<th>F</th>
<th>p-value</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N     Mean SD</td>
<td>N  Mean SD</td>
<td>N  Mean SD</td>
<td>2,752</td>
<td>4.412</td>
</tr>
<tr>
<td>O2-A1</td>
<td>REM</td>
<td>173    4.34 1.25</td>
<td>351 4.49 1.23</td>
<td>231 4.19 1.15</td>
<td>2,752</td>
<td>4.412</td>
</tr>
<tr>
<td></td>
<td></td>
<td>188    4.24 1.18</td>
<td>384 4.42 1.24</td>
<td>245 4.17 1.16</td>
<td>2,814</td>
<td>3.679</td>
</tr>
<tr>
<td>O1-A2</td>
<td>REM</td>
<td>187    4.09 1.20</td>
<td>382 4.15 1.10</td>
<td>243 3.87 1.08</td>
<td>2,809</td>
<td>4.847</td>
</tr>
<tr>
<td>C3-A2</td>
<td>REM</td>
<td>187    4.29 1.15</td>
<td>382 4.24 1.09</td>
<td>243 3.97 1.10</td>
<td>2,809</td>
<td>5.59</td>
</tr>
<tr>
<td>C4-A1</td>
<td>REM</td>
<td>187    3.92 1.17</td>
<td>351 3.95 1.11</td>
<td>231 3.70 1.03</td>
<td>2,752</td>
<td>3.925</td>
</tr>
<tr>
<td></td>
<td></td>
<td>173    3.84 1.01</td>
<td>382 3.86 1.04</td>
<td>243 3.63 1.00</td>
<td>2,809</td>
<td>4.09</td>
</tr>
</tbody>
</table>

One-Way ANOVA on z-score standardized measurements; SD: standard deviation; df: degrees of freedom (between groups, within groups); Adjusted p-value by sex, age, BMI and European ancestry proportion in general linear models.

a Bonferroni post hoc test for AG x GG: p=0.041
b Bonferroni post hoc test for AG x GG: p=0.023
c Bonferroni post hoc test for AA x GG: p=0.018; for AG x GG: p=0.020
DISCUSSION

Several previous studies revealed the interaction of Homer proteins with metabotropic glutamate receptors and the potential role of these proteins in the trafficking and/or clustering of the receptors in various cell types (4,20-23). Studies interfering with the normal expression of \textit{HOMER} genes suggest the involvement of these gene products in animal behavior, from \textit{Drosophila} to mammals (5). Also, genetic variation in \textit{HOMER1} seem to be associated with drug dependency and abuse (11) and mental disease (10).

In the present study, we report the association between rs3822568 in the \textit{HOMER1} gene with sleep latency, sleep efficiency, number of arousals per hour, AHI and theta spectral power in healthy subjects. The analyzed SNP consists of a genetic variant found at the 3’ untranslated region (3’UTR) of the \textit{HOMER1} gene, for which the ancestral allele is a guanine (G) and the alternative allele is an adenine (A).

Here, we found that homozygous individuals for the G allele, on average, experience higher sleep latency times, lower sleep efficiency, less arousals per hour and lower AHI than subjects carrying the A allele. This suggests that the presence of the G allele is associated with changes in sleep onset – leading to the higher latency times – but not the sleep maintenance – since no associations with arousals per hour were found. In this sense, the observed lower sleep efficiency might be attributed to the long sleep latency rather than to a higher sleep fragmentation caused by many arousals during the sleep time (24,25).

On the other hand, even if AHI is a common measure for the diagnosis and severity determination of OSAS, rs3822568 did not show any association with the presence of the syndrome according to the definitions we used (15). This corroborates that other factors besides the genetic background might influence the manifestation of the obstructive sleep apnea syndrome, such as environmental and developmental factors (26). Another aspect that needs to be taken in consideration is that the definition of hypopnea is not consensual among sleep researches (27), and some studies suggest than an AHI cutoff of 5 is too low, especially for elderly people (28). Moreover, we also observed that gender, age, BMI and genetic ancestry might influence the association between the investigated polymorphism and sleep traits, except sleep latency.

It is known that oscillations in the sleep EEG reflect the homeostatic regulation of sleep (29). Common variation in genes involved in sleep homeostasis has been associated with sleep-related traits.
Mazzotti and colleagues (16) found an association between a SNP in the adenosine deaminase gene and higher delta and theta EEG spectral powers, indicating a higher sleep intensity in carriers of the alternative allele. In our investigation, we observed that GG genotype carriers showed, on average, lower theta spectral power in stages 1, 2 and REM sleep – the associations remained significant only in the occipital derivations and in stage 1 and REM sleep after the adjustment for potential confounders (Table 2). These findings add on the results regarding the association between GG genotype and lower sleep efficiency, and suggests that changes in EEG power associated with this SNP might explain the differences found in sleep efficiency.

Naidoo and colleagues (30) demonstrated Homer1 upregulation during wakefulness and its down regulation at sleep is not a simple correlate, but a matter of cause and effect. Using Drosophila and mouse models, these authors showed that Homer1a/homer1a knockout leads to reduced and fragmented sleep in flies, while it causes inability to sustain the wake state in the rodents. Thus, it is possible that genetic variation in the Homer genes could modulate the subtle balance of HOMER proteins in the regulation of glutamatergic neurotransmission and yield different states of neuronal excitability in the nervous system, affecting sleep.

Polymorphisms in the Homer genes could, therefore, modulate the interactions among HOMER proteins in regulating glutamatergic neurotransmission and yield different states of neuronal excitability in the nervous system affecting sleep state. Considering that the 3’UTR is a key post-transcriptional regulation site, figuring a target for non-coding RNA based regulatory mechanisms such as microRNAs (31), polymorphisms at the 3’UTR may lead to a differential regulation of gene expression (32). This could explain the functional consequences of the studied SNP on variability of sleep-related traits presented in this study.

In summary, the present findings suggest that the rs3822568 polymorphism in the Homer1 gene might have an impact on sleep quality and sleep structure, as evidenced by higher sleep latency and lower EEG theta power in individuals carrying the GG genotype. Thus, this SNP may be an important source of variation in sleep homeostasis, probably due to the regulation of the glutamatergic signaling pathways.
ACKNOWLEDGMENTS

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Deaminase Polymorphism Affects Sleep EEG Spectral Power in a Large Epidemiological Sample.

leucocyte antigen DQB1*0602 allele is associated with electroencephelograph differences in


