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Original Article

Familial aggregation and heritability of insomnia in a community-based study

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ABSTRACT

Background: Emerging data suggested a significant familial aggregation of insomnia. We aimed to clarify the familial aggregation and heritability of insomnia disorder by using structural clinical interviews for the ascertainment of insomnia and psychiatric disorders in a community-based sample.
Methods: Seventy-five adolescents with insomnia and their 180 first degree relatives, together with 141 age- and sex-matched non-insomnia controls and their 382 first degree relatives, were recruited. Each subject underwent a structured clinical interview and completed a series of psychometric inventories. The rates of insomnia disorder among the first degree relatives were employed to analyze familial aggregation. Heritability of insomnia was analyzed by SOLAR program as based on father–mother-offspring trios.
Results: Our study confirmed a significant familial aggregation of insomnia with a first degree relatives' recurrence risk of 2.33 for current insomnia and 2.82 for lifetime insomnia, respectively. The heritability ± SE of current and lifetime insomnia disorder was 0.48 ± 0.13 and 0.61 ± 0.11 ($p < 0.001$), respectively, which were higher than insomnia symptoms as estimated by the Insomnia Severity Inventory (h^2 ± SE = 0.27 ± 0.09) and the Pittsburgh Sleep Quality Index (h^2 ± SE = 0.30 ± 0.11). After exclusion of comorbid psychiatric disorders, the heritability for current and lifetime primary insomnia was 0.45 ± 0.17 ($p = 0.007$) and 0.58 ± 0.21 ($p = 0.004$), respectively.
Conclusions: Our study demonstrates a significant familial aggregation with a high heritability of insomnia disorder. The strong heritability of insomnia persists despite the exclusion of psychiatric disorders. Further molecular genetic investigation of insomnia is indicated.
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1. Introduction

Family studies play a critical role in genetic epidemiology by delineating the familial aggregation and etiological association of a disorder [1–3]. In addition, identification for familial risk of a disorder may provide key components for treatment and prevention programs that target the family as a whole [4]. There have been, however, only limited family studies of insomnia, and a majority of them were conducted on adults in western countries [5–9]. In general, these studies reported familial aggregation of insomnia with several characteristics. First, two studies showed that earlier-onset insomnia (childhood-onset or earlier than 40 years old) seem to have stronger familial aggregation when compared with their counterparts [6,7]. Second, primary insomnia has a greater prevalence of positive family history of insomnia than insomnia related to psychiatric disorders and normal sleepers [9]. Third, our previous study showed a dose–response effect for parental insomnia on the rate of insomnia of their children with a slight predilection of maternal influences [10]. Finally, results from twin studies suggested that heritability would potentially account for a high proportion of the variance (42–57%) in insomniac symptoms [11–16]. Nonetheless, the current literature is limited in several aspects. First, none of the family/twin studies employed a structured clinical interview to confirm the diagnosis of insomnia and the associated mental disorders among both probands and their family members. The accuracy of self-reported family history varies across different disorders. A recent report from the National Institutes of Health suggested that family history has a relatively high specificity (90–95%) but varies in degrees of sensitivities (6–95%), especially for mental illness (sensitivity ranging from 6 to 82%) [17]. Family history will be overestimated with increased frequency of the disorder, increased number of relatives, and for diseases with earlier age of onset [18]. For this reason, the absence of clinical assessments of family members might have biased the studies. Second, only two studies (including our previous study) employed control subjects to compare the recurrence risk of insomnia in family members

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[8,10]. Further study is warranted to confirm the familial clustering of insomnia.

Several underpinning mechanisms might contribute to the familial aggregation of sleep disorders, which might include genetic predisposition, shared environmental risk factors, medical and psychiatric co-morbidities, and learned behaviors [2,4,10]. Several environmental and socio-economic factors are correlated with the occurrence of insomnia among family members in our previous study [10]. The familial clustering, however, is maintained even after controlling for these factors, which suggests that the familial aggregation of insomnia is not entirely mediated by environmental factors [10]. The molecular genetic analysis of the pathogenesis of insomnia is limited. A study of primary insomnia has shown that a missense mutation of GABAAβ3 is only found in one out of 112 insomniac subjects [19]. Recently, another association study has reported that the short allele of the Serotonin Transporter Length Polymorphism (5-HTTLPR) is significantly associated with primary insomnia in a German sample, but with a relatively small odds ratio of 1.34 [20].

Thus, previous studies suggest that both environmental and genetic factors contribute to the pathogenesis of insomnia [10,19,20]. In this study we aimed to: (1) confirm the familial aggregation phenomenon of insomnia by a population-based case-control study; (2) estimate the heritability of insomnia (potential contribution by genetic factors) by a study with a father–mother-offspring trios design.

2. Materials and methods

2.1. Subject selection

The protocol of this study was approved by the Institutional Ethics Review Committee. All participants under 18 years old gave written assents and parental consents. Participants aged 18 or above gave their own written consent. The current study was part of an ongoing epidemiologic study about sleep problems among Hong Kong Chinese children and their parents, which started in 2003–2004 (baseline) [10,21–24]. A follow-up study was conducted during 2008–2011 and a total of 1611 adolescents with 2641 parents and 1055 siblings were recruited [10,25,26]. The families of the current study were recruited from the samples of this cohort. We employed a stratified sampling procedure for selection of subjects (for more details on the subjects' recruitment and assessment please also refer to our previous paper [27]). In brief, all adolescents with complaints of insomnia (difficulty initiating sleep [DIS], difficulty maintaining sleep [DMS], or early morning awakening [EMA]) of at least three times/week or usual sleep onset latency $\geqslant$30 min over the past 12 months were invited to attend the family study with detailed clinical measures. These subjects were classified as high-risk subjects. Adolescents without any insomnia symptoms (<3 times/week) and with a usual sleep onset latency <30 min in the past 12 months were randomly selected as low-risk controls. All of their biological parents and full siblings over six years old were also invited to attend the current study. Please refer to our previous publication and online supplement for more details concerning sample recruitment and ascertainment [27].

2.2. Methods

Each subject underwent a face-to-face structured clinical interview and examination and completed a series of psychometric inventories. The interviewing clinicians were blind to the initial classification of the subjects (high or low risk). In order to diagnose the comorbid psychiatric disorders, the Structured Clinical Interview for the DSM-IV Axis I Psychiatric Disorder (SCID-I) was employed for both parents and siblings over 18 years old [28,29], while the Diagnostic Interview Schedule for Children-Version 4 (DISC-IV) was employed for adolescents and their siblings below 18 years old [30].

The diagnosis of insomnia was determined by interviewing psychiatrists on the basis of the Diagnostic and Statistical Manual of Mental Disorders, the fourth edition (DSM-IV) criteria for insomnia disorder [31], which includes: (1) a predominant complaint of difficulty initiating or maintaining sleep or early morning awakening for at least one month; (2) causes a significant distress or impairment in social, occupational (or academic in adolescents), or other important areas of daytime functioning. Non-restorative sleep (NRS), which was proposed as another subtype of insomnia by DSM-IV [31], was not recruited into the analysis, as NRS has overlapping association with other sleep disorders such as sleep deprivation and sleep apnea syndrome [32–34]. The inclusion of NRS might potentially increase the heterogeneity of the study samples. Both lifetime and current episodes of insomnia were determined by clinical interviews.

2.3. Severity of insomnia

The severity of insomnia was assessed by the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI). The ISI is a 7-item questionnaire assessing the subtype, severity, and impact of sleep difficulties in the past two weeks with satisfactory psychometric properties [35]. The PSQI is a 19-item questionnaire evaluating sleep quality and disturbances over a one-month interval [36]. Higher scores in the ISI and PSQI indicate more severe insomnia symptoms and poorer sleep quality, respectively.

2.4. Assessment of depressive and anxiety symptoms

The validated Chinese version of the Hospital Anxiety and Depression Scale (HADS) was employed to assess the depressive and anxiety symptoms of both adolescents [37] and adults [38]. The HADS consists of seven items for depressive symptoms and seven items for anxiety symptoms, which are assessed by a four-point Likert scale ranging from zero to three. Higher scores suggest a higher level of depression or anxiety.

2.5. Sample size estimation

To achieve a power of 80% and a type I error of 0.05 and an odds ratio of 2.5 in the familial risk (based on our previous study [10]), we estimated that the minimum sample size required for this study would be 75 case-families and a comparable or higher number of control-families to detect significant familial aggregation.

2.6. Statistical methods

Descriptive statistics were presented as percentages for discrete variables and as means (standard deviation) for continuous variables. The comparisons between insomniacs and non-insomniacs with respect to socio-demographic and clinical characteristics were performed by independent sample *t*-test, Mann–Whitney *U* test, and chi-square test when appropriate. To analyze the familial aggregation for dichotomized traits, odds ratios were estimated by the Generalized Estimating Equation (GEE) model to investigate the familial clustering of insomnia after adjusting for age, gender, and psychiatric disorders. A *p*-value of less than 0.05 was considered to be a statistically significant level. SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all tests except for heritability analysis.

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