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Genetic and Demographic Predisposing Factors Associated with Pediatric Sleepwalking in the Philadelphia Neurodevelopmental Cohort

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Abstract

Objectives: Sleepwalking is a parasomnia associated with non-rapid eye movement (NREM) sleep and is formally diagnosed using polysomnography (PSG). However, PSG are difficult to perform on children or adolescents due to needed compliance. To understand this condition in youth, few studies have been conducted on a large cohort of youths with a diverse distribution of ages and races to characterize it better in the absence of PSG. The present study aimed to evaluate the prevalence of sleepwalking in youth, as well as associated demographic and genetic characteristics, using questionnaires in a large pediatric cohort.

Methods: Data from the Philadelphia Neurodevelopmental Cohort (PNC) of 7515 youths aged between 8 and 22 years were used in analyses. Demographic and clinical data, including age, sex, and race, and genetic data from 2753 African American (AA) and 4762 European American (EA)

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subjects were investigated. The age-wise prevalence of sleepwalking in AA and EA subjects was evaluated. Finally, race-specific genomewide association (GWAS) analyses of sleepwalking were also performed (N=155 AA cases and 2598 AA controls; N=512 EA cases and 4250 EA controls).

Results: Lifetime history of sleepwalking correlated with male sex and EA race. A genetic risk locus that reached genome-wide significance was detected at rs73450744 on chromosome 18 in AA, but not EA youth.

Conclusion: The present results suggest that male sex, EA race, and genetic factors may be associated with higher rates of sleepwalking among youth. Future studies should consider these variables to advance understanding of the complex pathogenesis of sleepwalking.

Keywords

disorders of arousal; Sleepwalking; pediatric parasomnia; race; GWAS

1. INTRODUCTION

Sleepwalking is a type of parasomnia observed in children,[1,2] and is characterized by complex behaviors that are generally initiated during partial arousals from slow wave sleep. The representative episode is comprised of a range of behaviors, such a toddler sitting up and crawling around the bed, walking quietly, or running around the house. The sleepwalking individual is disoriented in time and space, with slow speech, severely diminished mentation, and blunted responses to questions or requests.[3] Sleepwalking, sleep terrors, and confusional arousal are classified as disorders of arousal (DOA) in the International Classification of Sleep Disorders third edition (ICDS-3), and are considered to be provoked by the dissociation of non-rapid eye movement (NREM) sleep into wakefulness. Sleepwalking is diagnosed based on clinical criteria, such as recurrent episodes of incomplete awakening from sleep, inappropriate or absent responsiveness to the efforts of others to intervene or redirect the person during the episode, limited or no associated cognition or dream imagery, and partial or complete amnesia for the episode, and arousals are associated with ambulation and other complex behaviors out of bed.[3] Importantly, sleepwalking may be associated with a risk of injury and may be life threatening due to the unconscious performance of dangerous behaviors.[4] However, most children with sleepwalking do not require treatment because it naturally resolves with age, which either suggest that the mechanisms underlying sleepwalking likely correspond to brain plasticity or represent transient deviations in sleep regulation in otherwise typically developing youth. [1,3–5]

A pathophysiological model of DOA has broadly been described using the 3-P model, in which DOAs are attributed to the co-occurrence of various predisposing, priming, and precipitating factors.[6,7] Although priming and precipitating factors can be identified by sleep deprivation, various substances including Z-drugs, comorbid conditions, or arousing external stimuli, an assessment of predisposing factors requires evaluation in large cohorts. Moreover, predisposing factors precede the emergence of sleepwalking and may be related to genetic factors that have yet to be confirmed. Indeed, sleepwalking runs in families and manifests in the children of parents who sleepwalk.[8–10] A twin study reported a

significantly higher concordance of sleepwalking in monozygotic pairs than in dizygotic pairs.[11,12] In addition to essential and detailed interviewing of children and their parents, polysomnography (PSG) is performed for comprehensive examination of sleep comorbidities (e.g. sleep apneas) and to explore various differential diagnoses (e.g. sleep epilepsy). However, PSG is not practical to conduct in large pediatric cohorts due to requisite hospitalization. Further, since sleepwalking does not always occur during a PSG, even an overnight PSG may not be sufficient to capture sleepwalking events, complicated further by poor compliance in youth. Consequently, few studies have been conducted to characterize factors predisposing youth to sleepwalk in a large enough cohort with diverse distributions of ages and races to be able to generalize toward a population based understanding of those predispositions.[13]

Data from the Philadelphia Neurodevelopmental Cohort (PNC) is publicly accessible from the National Institutes of Health database of Genotypes and Phenotypes (dbGap).[14,15] It includes a large sample of nearly 10,000 African (AA) and European American (EA) youths evaluated in the Children's Hospital of Philadelphia (CHOP) network. This cohort provides multi-level information on youth ranging from demographic, to behavioral, and genetic. Although the PNC was not designed to specifically study sleep, the database includes a questionnaire that reports on the presence or absence of sleepwalking among youth to permit an exploratory investigation of demographics and genetic factors associated with the presence or absence of sleepwalking in a large cohort of youth. Thus, this study aimed to examine predisposing factors, namely, demographic and genetic factors, for sleepwalking based on data derived from the PNC database using statistical and genome-wide association (GWAS) analyses. This characterization may provide initial insights into the pathogenesis and treatment of sleepwalking in youths.

2. METHODS

2.1 Sample

Data in the PNC database were collected from the CHOP healthcare network. Subjects were not specifically recruited from psychiatric or sleep specialty clinics. Inclusion criteria were youths that were ambulatory, in stable health, proficient in English, and able to complete the study procedure, including neurocognitive, genetic, and clinical assessments. Youths with severe developmental delays, significant hearing loss, or limited mobility were excluded. Our requests for the research projects were approved and listed in the requester name of Yuhei Chiba and Manpreet Sigh in https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000607.v3.p2&phv.

2.2 Data assessment

Data analyses of 8719 subjects (ages: 8-22 years) from the PNC phs000607.v1.p1 were conducted. Demographic factors and medical histories were assessed using a structured computerized instrument, namely the GOASSESS.[16,17] We investigated the age, sex, and race as self-reported by AA and EA subjects, excluding 1061 subjects of mixed/other races to simplify the GWAS analysis. GOASSESS is designed to collect information on the past and present history of medical condition including sleepwalking, and was administered to

subjects over 11 years of age, as well as their parents if subjects were between the ages of 8 and 17 years. PNC youth or their parents were asked “Have you (your child) ever had sleepwalking?”. More detailed questions were not asked on sleepwalking. Responses were coded as yes, no, or unsure. If the answer was yes, the follow-up question “Is it a current condition?” was added. Further information was not obtained on the “current condition”. After the exclusion of 143 subjects who responded “unsure” to the first question, the remaining 7515 subjects who were AA (2753 cases) and EA (4762 cases) were examined. Subjects who responded “yes” to the first question by themselves or via their parents were defined as those with a history of sleepwalking. Subjects who responded “no” by themselves or via their parents were defined as subjects without a history of sleepwalking.

2.3 Analysis of demographic factors associated with sleepwalking

In the analysis of all subjects, we compared the prevalence of sex, age, and EA using the Student’s *t*-test and chi-squared test, and then calculated the odds ratio using a univariate regression analysis between subjects with and without a history of sleepwalking.

The prevalence of sex and age in AA and EA youths were compared using the Student’s *t*-test and chi-squared test, and then the odds ratio between subjects with and without a history of sleepwalking was calculated using a univariate regression analysis. The lifetime and current prevalence of sleepwalking were compared between AA and EA youths.

The current age-wise prevalence of sleepwalking was plotted against race. The age-wise prevalence of current sleepwalking was compared between AA and EA subjects using Fisher’s exact test and False Discovery Rate correction of Benjamini & Hochberg method. Statistical analyses were performed using SPSS v 20.0 (IBM Corp., Armonk, NY, USA). The level of significance was set to $p < 0.05$.

2.4 Genetic factors of sleepwalking: A GWAS analysis

All blood samples were genotyped on one out of four Illumina arrays: HumanHap550v3, HumanHap550v1, HumanHap610, and Omni Array. Genotype data were imputed using the IMPUTE2 package[18] and reference haplotypes in Phase III of the 1000 genomes data (October 2015 release)[19] included approximately 88 million variants from 2,504 individuals from Africa, Asia, Europe, and the Americas. Excessive relatives with a pairwise proportion of identity by the descent estimate of PI_HAT > 0.25 were excluded. We conducted a principal component analysis (PCA) in PLINK1.9,[20] and calculated eigenvectors. A quality control process was performed to eliminate individuals with >2% missing data and SNPs with >1% missing data, minor allele frequencies (MAF) <0.01, and Hardy-Weinberg Equilibrium p values $<10^{-6}$.

In the SNP-based association analysis, a logistic regression with the covariations of sex, age, and the first four eigenvectors calculated by the PCA was applied using an additive effect model between AA and EA subjects with and without a history of sleepwalking. A meta-analysis to combine p values from the GWAS analysis of AA and EA subjects was performed using a fixed-effect model with the --meta command of PLINK1.9. A QQ plot and lambda were calculated for GWAS and the meta-analysis using the R qqman[21] and GenABEL[22] packages. Genome-wide significance was set to $P < 5\times10^{8}$. Regional

association plots were generated using LocusZoom.[23] (http://locuszoom.org/) by summary statistics from GWAS and the meta-analysis. We selected the "1000 Genomes Nov 2014 AMR" panel for the background LD structure.

3. RESULTS

3.1 Investigation of demographic factors

The results obtained on demographic factors are summarized in Table 1.

3.1.1 Prevalence of sleepwalking by race—The numbers of AA and EA subjects with sleepwalking during their lifetime were 155 (lifetime prevalence: 5.6%) and 512 (lifetime prevalence: 10.8%), respectively; therefore, 667 subjects (lifetime prevalence: 8.9%) had a history of sleepwalking. The numbers of AA and EA subjects currently sleepwalking were 44 (current prevalence: 1.6%) and 155 (current prevalence: 3.3%), respectively; therefore, 199 subjects were currently sleepwalking (current prevalence: 2.6%). The numbers of AA and EA subjects without a history of sleepwalking during their lifetime were 2598 and 4250, respectively, with a total of 6848.

3.1.2 Odds ratio of sleepwalking with demographic factors.—A history of sleepwalking correlated with male sex (odds ratio, 1.30) and EA race (odds ratio, 1.76). In AA and EA subjects, a history of sleepwalking correlated with male sex (odds ratios of 1.56 in AA and 1.23 in EA, respectively). The lifetime prevalence of sleepwalking was significantly higher in EA subjects than in AA subjects (10.8 and 5.6%, respectively, $P<0.001$ by the chi-squared test). The current prevalence of sleepwalking was significantly higher in EA subjects than in AA subjects (3.3 and 1.6%, respectively, $P<0.001$ by the chi-squared test).

3.1.3 The current prevalence of sleepwalking by age.—The current prevalence of sleepwalking was plotted against age in Figure 1 and detailed in Table 2. The current prevalence of sleepwalking in all subjects included in the analysis was the highest at approximately 4.5% in eight-year-old subjects, and gradually decreased with age; however, a transient increase was observed at approximately 18 years old. No significant differences at any ages by Fisher exact test were observed in the age-wise current prevalence of sleepwalking between AA and EA subjects, except at the age of 18 years old, with the current prevalence of sleepwalking being significantly higher in EA subjects than in AA subjects. But this significance resulted in lost by FDR correction using the Benjamini & Hochberg method. The characteristics of a bimodal distribution were apparent in EA subjects

3.2. GWAS analysis

Due to the small sample size for analysis, we performed a GWAS analysis of AA and EA subjects combined with and without a history of sleepwalking. Figure 2a and b show a Manhattan plot and QQ plot of the GWAS analysis of AA and EA subjects with the covariates of age, sex, and the top 4 eigenvectors of PCA. The lambda values of AA and EA analyses were 0.971 and 1.013, respectively. Figure 2c shows a Manhattan plot and

QQ plot of the meta-analysis of GWAS of AA and EA subjects. The lambda value of the meta-analysis was 1.009. Table 3 summarizes representative SNPs related to sleepwalking based on the results of the GWAS analysis and meta-analysis. A genetic locus that reached Genome-wide significance at $P< 5\times10^{-8}$ was detected at rs73450744 on chromosome 18 in the AA analysis. A locus zoom plot showed that rs73450744 was in a non-coding region and the nearest gene was Keratoconus Gene 6 (KC6). (Figure 3) Since EA subjects did not have this SNP, it showed no significance in the meta-analysis. Although rs1201967 and rs12197808 exhibited the lowest p values in the meta-analysis, these values did not reach Genome-wide significance.

4. DISCUSSION

We investigated the prevalence of sleepwalking and predisposing demographic and genetic factors in a cohort of 8-22 year old youth. Our results showed that the prevalence of sleepwalking is higher in EA subjects than in AA subjects in the PNC database, and that key SNPs were associated with sleepwalking in AA but not EA youth. The PNC study very broadly queried whether sleepwalking was present or absent in a subject based on their response to a structured computerized instrument, and subjects and their parents received no additional information on the definition of sleepwalking as a sleep disorder, its duration, severity, or frequency, and which informant (parent/child/both) provided information about sleepwalking. Subjects are usually not aware of their episodes unless episodes are witnessed and reported by others. Stallman et al., [24] performed a self-report investigation on sleepwalking, which showed that the 17.5% of 532 Australian adolescents, mean age = 17.0 years old, were unsure if they had sleepwalking in the previous month. The existence of current sleepwalking might be biased by the fact that some participants might experience recall bias or live alone, limiting the ability of others to witness or observe sleepwalking episodes. Reports on the detailed episodes of sleepwalking, sleep habits, socioeconomic status, sleep parameters, drug intake, and family history of sleepwalking are important to contextualize and confirm our findings. Our study provides a preliminary report on the key demographic and genetic predispositions that might merit consideration.

4.1 The prevalence of sleepwalking by race.

The lifetime prevalence of sleepwalking was approximately 9% in the PNC, with a current prevalence of sleepwalking of 2.64% across all youths examined in this cohort. Stallman and Kohler conducted a meta-analysis of the prevalence of sleepwalking,[13] and the findings obtained showed that the estimated lifetime prevalence of sleepwalking was 6.9%, while the current prevalence of sleepwalking (within 12 months) was 5.0% in children and adolescents younger than 18 years old. They noted that the prevalence of sleepwalking was affected by the definition of each sleepwalking-focused study and the methods used to assess a history of sleepwalking, such as self- or parental reports, the frequency of episodes, recall periods, types of behavior, and the presence of impairment or distress. Our results also showed that lifetime and current prevalence of sleepwalking were significantly higher in EA subjects (10.75 and 3.25%, respectively) than in AA subjects (5.63 and 1.60%, respectively), suggesting that there may be race differences in the prevelance rates of sleepwalking across race. To our knowledge, our analyses are the first to characterize

sleepwalking in AA children and adolescents. Indeed, our findings among youth mimic those previously reported in adults [25] in which AA adults had a lower odds ratio of sleepwalking than EA adults. Others [26] have also shown that the lifetime prevalence of sleepwalking is roughtly 4.3% in young Nigerian adults aged 19-35 years old, which was similar to the rates observed in AA youths in the PNC. In our univariate logistic regressions, EA race determined higher odds of sleepwalking compared to AA race. Guglielmo et al.[27] elaborates on sleep characteristics in US school-aged children and adolescents, reporting more frequent sleep/wake issues and earlier despite longer sleep duration in EA compared to AA youths. These sleep characteristics were independent of the socioeconomic status, such as parent education, income, or poverty. Finally, Rao et al.[28] has reported differences in the electroencephalographic sleep patterns of adolescents by race. Specifically, AA youth showed lower sleep efficiency, spent more time in stage 2 sleep, and had less slow wave sleep compared to EA youths. Although the socioeconomic status of the PNC was not reported nor was a PSG performed, American youth of EA descent may have sleep habits that are related to deeper sleep and sleep fragmentation, resulting in an increased risk of sleepwalking compared to AA youth.

4.2.1 Sex differences—The present study showed a history of sleepwalking significantly correlated with male sex. There are some mixed reports about sex differences in sleepwalking. Archbold et al.[29] collected data from a pediatric sleep questionnaire from the parents of 1038 children (58.4% European American, 19.4% African American) aged 2.0 to 13.9. Boys showed significantly higher rate of lifetime sleepwalking (boys of about 17% and girls of about 12%), which is consistent with our results. In contrast, Petit et al., [10] performed questionnaires in mothers of 1940 children aged under 13 in Canada, and sex was not associated with the occurrence of sleepwalking during childhood. In addition, Laberge et al.,[30] provided data from mothers of 1333 children aged under 13 in French, and sex was not associated with the occurrence of sleepwalking during childhood. Considering brain maturation by sex differences, prior studies have reported that girls display a higher overall proportion of slow wave sleep during the night than boys; however, the amount of stage 4 sleep decreases during development with a steeper slope in boys than in girls.[31,32] These differences in the sleep architecture between boys and girls and over the course of development may explain sex differences in the prevalence of sleepwalking.

The PNC cohort contains information from many clinical evaluations, including the dimensionally granular phenotyping of cognitive and neurodevelopmental characteristics, which may be the focus of future studies to elucidate sex differences between sleepwalking, neurodevelopment, and sleep maturation.

4.3 Age-wise prevalence of sleepwalking

As expected, the prevalence of sleepwalking in EA and AA subjects generally decreased with age, likely reflecting a mechanism by which youth outgrow this problem over the course of development. In our study, current prevalence of sleepwalking in EA subjects showed a bimodal distribution, with a continuous decrease from 8 years old followed by a transient increase at approximately 18 years old. However, the age-wise differences of

current prevalence of sleepwalking between EA and AA were not significant. There are few previous reports on age wise prevalence of sleepwalking. Klackenberg and colleagues,[33] investigated the age-wise current prevalence of sleepwalking in subjects aged between 6 and 16 years of age in Sweden. The prevalence of “sometimes or often sleepwalking” was the highest at eight years old and then decreased with age, but slightly increased at 15 and 16 years old, which looked consistent with our result of EA youth in the PNC. Fisher and Wilson[34] also reported the age wise prevalence of current sleepwalking of youth under 20 years old in Canada, which demonstrated that the current prevalence decreased by age and transient slight increase at 17 and 18 years old, consistent with our result. Longitudinal relations between brain maturation and sleep architecture change may impact the pathophysiology of sleepwalking[31,32].

4.4 Genetic predisposition

Our GWAS analysis identified one locus on chromosome 18 that predicted sleepwalking. These results need to be replicated in a larger sample with controls because the number of cases with lifetime sleepwalking was small for a GWAS analysis (581 EA and 109 AA youths with sleepwalking). However, to our knowledge, our pilot analysis is the first to use a GWAS analysis of sleepwalking, and rs73450744 on chromosome18 reached genome-wide significance in AA youths with versus without a history of sleepwalking. Since this SNP was not present in EA youths, it was not possible to analyze the data using a meta-analytic approach.

The SNP rs73450744 is in a non-coding region and the nearest gene is KC6. Rabinobitz et al.[35] reported that the mRNA of KC6 increased in corneas with keratoconus, which is a non-inflammatory corneal thinning disorder affecting younger individuals. Eye rubbing is considered to be an etiology of keratoconus. However, the pathophysiology of keratoconus and the function or contribution of KC6 to keratoconus remain unknown. Waisberg et al.[36] reported a case of keratoconus that presented with sleepwalking. In this case, keratoconus was associated with eye rubbing and eye pressing during sleepwalking. Therefore, keratoconus appears to be a consequence of sleepwalking; however, the causal relation is unclear. Patients with keratoconus are also reported to be at an increased risk of developing obstructive sleep apnea,[37,38] suggesting another potential association between keratoconus and sleepwalking. keratoconus may represent a sleep fragmentation factor, which is a priming factor, according the 3-P model. Further investigations on the relations among keratoconus, sleepwalking, and obstructive sleep apnea are needed.

No SNPs reached genome-wide significance in our overall meta-analysis. Human Leukocyte Antigen (HLA) DQB1 allele was reported the risk for sleepwalking.[39,40] Unfortunately our typical GWAS method cannot determine the HLA type. Licis et al.,[41] investigated the inheritance of sleepwalking in 4 generations of a single pedigree, and identified the genetic locus for sleepwalking on chromosome 20q12-13.12. The locus of KC6 and other candidate loci explored in our study are not located on 20q12-13.12. These variations in findings may be attributed to population differences or study inclusion/exclusion criteria, such as the exclusion of excessive relatedness in the PNC compared to pedigree studies. Nevertheless, the presence of sleepwalking in family pedigrees underscore the need to consider genetic

contributions of this comlex phenotype, which like other neurodevelopmental conditions, may be more polygenic and multifactorial rather than monogenic or follow standard Mendelian patterns.

Although the results of the present GWAS analysis showed that KC6 reached genome-wide significance and had a relatively high odds ratio in AA youth, this variant is a low frequency variant that needs to be interpreted with caution. Low frequency variants will have a small effect at a population level. However, individuals carrying this risk variant may exhibit the sleepwalking phenotype. Unfortunately, no family histories are included in the PNC. Future studies are needed to investigate whether the expression of this gene increases or decreases in individuals currently sleepwalking combined with more information on family medical histories.

4.5 Limitations

The PNC is a large and diverse database of youth. We attempted to address challenges related to variance in race by only including the two largest race subgroups represented in the database (namely, AA and EA) in our analysis, while maintaining the value of diverse representation among participants. Although the overall cohort was large, the relatively smaller sample size for the GWAS analysis within race subgroups was a limiting factor, and may contribute to null findings (type I error) in EA youth and in the meta-analysis. The AA sample was even smaller, which raises a concern that the significant SNP may be the result of a type II error, and significant SNPs in small GWAS are very hard to replicate. Future studies including more subjects or combinations of cohort studies will be beneficial to confirm our preliminary observations of the effects of the genome on sleepwalking. Ultimately, this research merits replication in an even larger dataset aimed to evaluate multi-level sleep characteristics among a diverse group of children and adolescents.

5. CONCLUSION

Sleepwalking is prevalent among youth but tends to decrease in frequency with age. Further, sleepwalking may be associated with key predisposing demographic factors, including male sex and EA race. A significant genetic risk locus was identified at rs73450744 on chromosome 18 in exploratory analyses of AA youths. The regulation of sleep or sleepwalking behaviors themselves in youths may be altered by multiple factors. Although the pathogenesis of sleepwalking may be complex, our preliminary analysis points to potentially important demographic variables that may need to be considered in sleepwalking children. Additional studies examining the neurobiological etiology of sleepwalking will aid in translating toward novel and personalized treatments.

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Highlight

We explored the demographic and genetic characteristics of sleepwalking in 7515 youth.

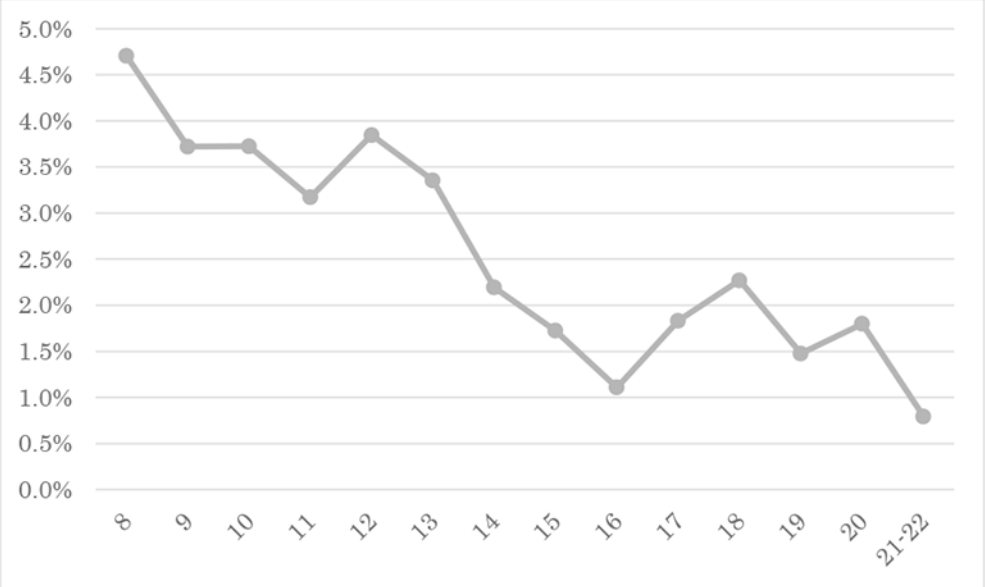
Sleepwalking is prevalent among youth but tends to decrease in frequency with age.

Male sex was associated with higher rates of sleepwalking among youth.

European American race was associated with higher rates of sleepwalking among youth.

A risk locus was identified in exploratory analyses of African American youths.

A. Prevalence of sleepwalking in all subjects



B. Prevalence of sleepwalking in African and European American subjects

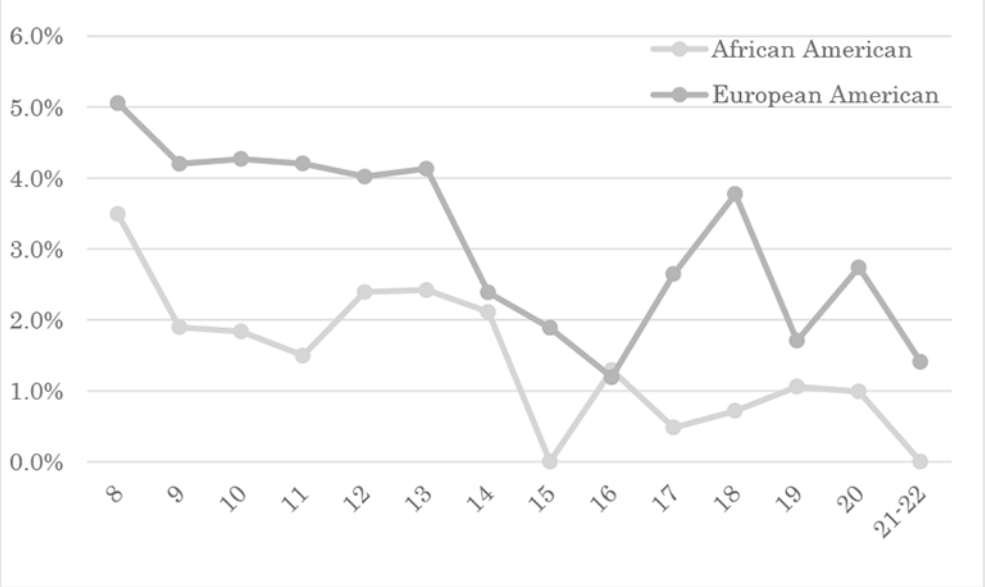


Fig. 1.

An age-specific plot of the current prevalence of sleepwalking.

*; Significantly different prevalence by Fisher's exact test between African and European American subjects.

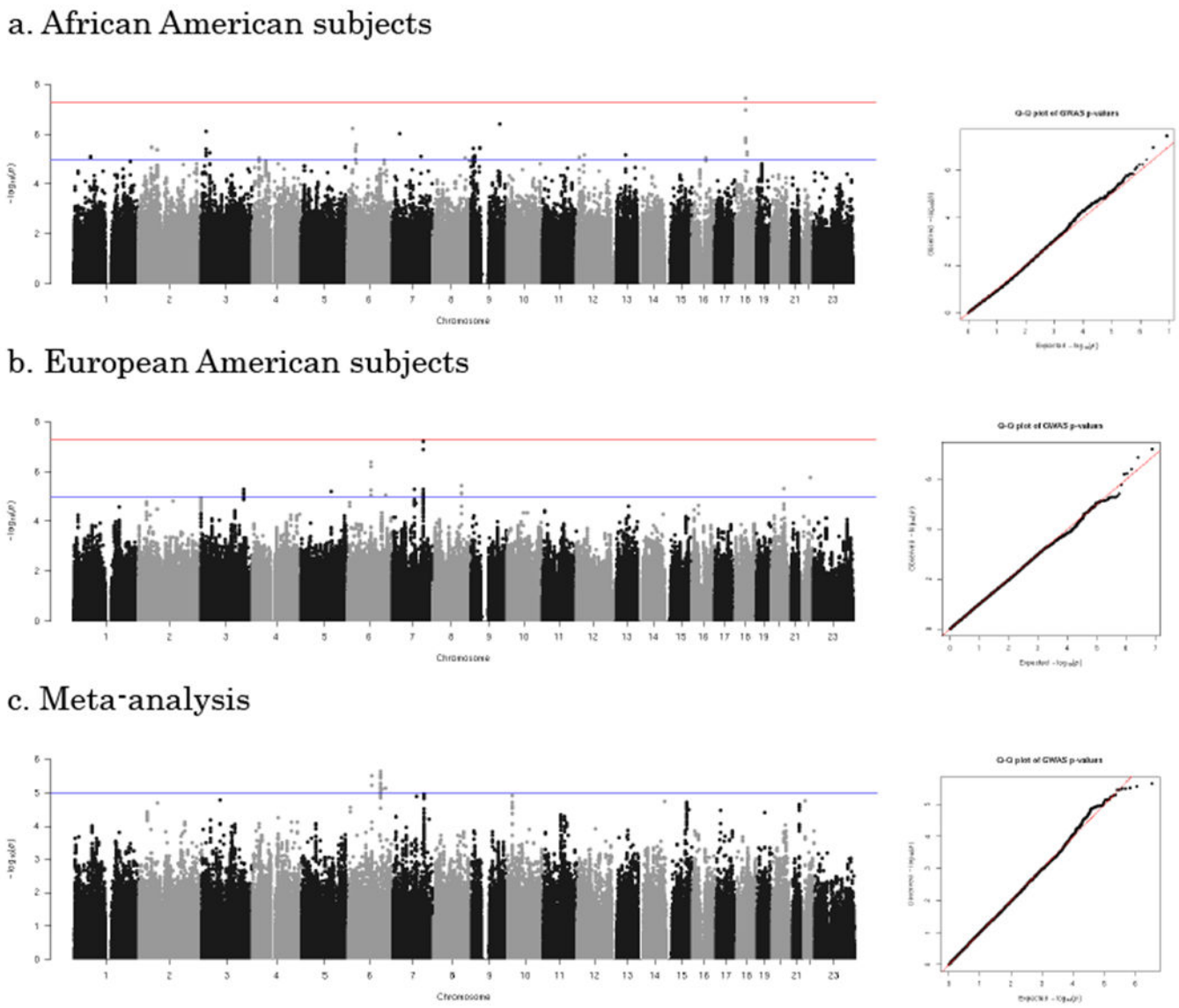


Fig. 2.

Manhattan plots of sleepwalking in African and European Americans. The SNP, rs73450744, on chromosome 18 in African American subjects reached genome-wide significance at $p < 5 \times 10\ 8$.

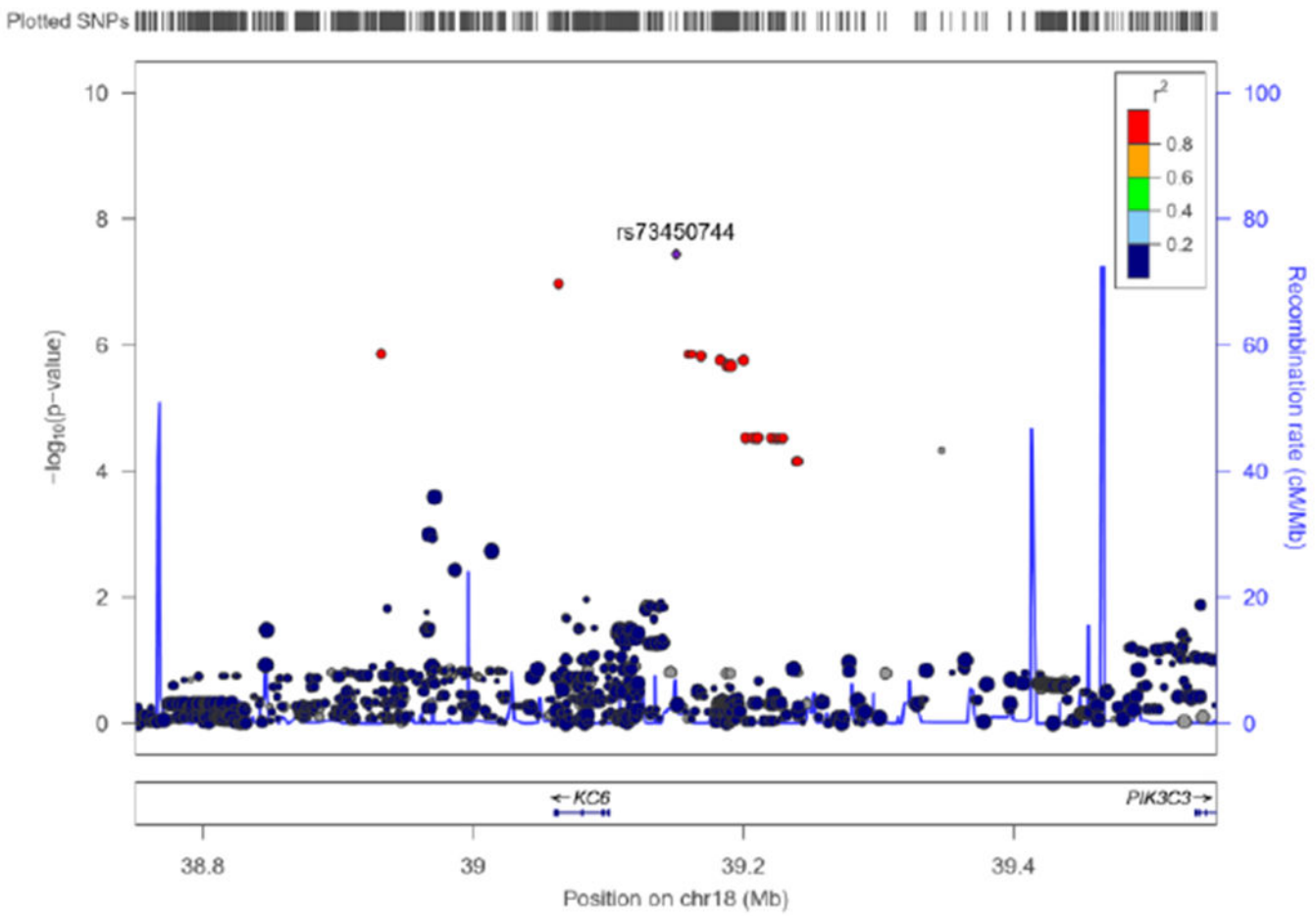


Fig. 3.

Locus zoom plot of GWAS of rs73450744 in African American subjects. The nearest gene of rs73450744 is KC6.

Table 1.

Demographic factors of all, African, and European subjects with and without a history of sleepwalking.

	All subjects (N=7515)			African subjects (N=2753)			European subjects (N=4762)		
	SW(+)	SW(−)	odds	SW(+)	SW(−)	odds	SW(+)	SW(−)	odds
Sleepwalking history (Number)	667	6848		155	2598		512	4250	
Male	55.2%	48.1%	1.30	56.1%	45.3%	1.56	54.9%	49.8%	1.23
Age (mean ± standard deviation)	13.8±3.7	13.8±3.7		13.3±3.7	13.9±3.7		14.0±3.7	13.8±3.6	
Race (European American)	76.8%	62.1%	1.76						
Lifetime frequency	8.88%			5.63% *			10.75%		
Current number	199			44			155		
Current prevalence	2.64%			1.60% *			3.25%		
Type of clinical interview									
Adult proband (18y.o.~)	21.7%	20.4%		19.4%	22.3%		22.5%	19.3%	
Middle proband (11 ~ 17 y.o.)	54.4%	55.2%		49.7%	54.0%		55.9%	55.9%	
Young proband parents (8~10 y.o.)	23.8%	24.4%		31.0%	23.7%		21.7%	24.9%	

The odds ratios of the items are shown when they correlated ($p<0.05$) with sleepwalking in a multivariate logistic regression analysis.

SW; sleepwalking, y.o.; years old

*; Significantly different prevalence between African and European American subjects.

Table 2.

Summary of the age-related current prevalence of sleepwalking.

Age	All subjects	African	European	P-value
8	4.52%	3.49%	5.06%	0.434
9	3.35%	1.90%	4.20%	0.226
10	3.33%	1.84%	4.27%	0.157
11	3.06%	1.50%	4.20%	0.062
12	3.62%	2.39%	4.02%	0.644
13	3.72%	2.42%	4.13%	0.644
14	2.28%	2.11%	2.39%	1.000
15	1.27%	0.00%	1.89%	0.058
16	1.23%	1.29%	1.19%	1.000
17	1.88%	0.48%	2.65%	0.108
18	**2.56%**	**0.72%**	**3.77%**	**0.013** *
19	1.45%	1.06%	1.71%	0.710
20	2.02%	0.99%	2.74%	0.651
21-22	0.89%	0.00%	1.39%	1.000

*; p value is < 0.05 by Fisher exact test, but is not significant when adjusted for multiple comparisons.

Table 3.

Summary of GWAS results

Results of GWAS														
CHR	**SNP**	**BP**	**A1/ A2**	**MAF in EA**	**MAF in AA**	**Case**	**Control**	**OR**	**P**	**Fq_case**	**Fq_control**	**Nearest Gene**		
African American														
3	rs113999746	21220365	A/ G	0.0001853	0.02285	109	1710	4.458	7.50E-07	0.07339	0.01849	VENTXP7		
6	rs183412314	20663830	T/ C	0.0002806	0.01127	109	1709	6.495	5.76E-07	0.05093	0.008269	CDKAL1		
7	rs493724	29007667	G/ C	0.00009259	0.02974	109	1710	3.641	9.18E-07	0.08716	0.02392	TRIL		
9	rs113394219	115184393	A/ G	0.0008329	0.07278	109	1710	2.822	3.63E-07	0.1667	0.0684	HSDL2		
18	rs73450744	39150106	T/ C	0	0.01529	109	1710	5.765	3.67E-08	0.06881	0.01267	KC6		
European American														
6	rs387722	92340664	C/ T	0.3708	0.4144	472	4001	0.6795	3.88E-07	0.2966	0.3778	CASC6		
7	rs157658	121798998	T/T	0.4534	0.3422	472	4001	0.679	6.21E-08	0.3715	0.4641	AASS		
Meta-analysis														
CHR	**SNP**	**BP**	**A1/ A2**	**MAF in EA**	**MAF in AA**	**Case**	**Control**	**OR**	**P**	**Fq_case**	**Fq_control**	**Q**	**I**	**Nearest Gene**
6	rs1201867	92340802	T/ G	0.3689	0.224	581	5710	0.7222	3.03E-06	0.2814	0.3306	0.0734	68.79	CASC6
6	rs12197808	125201579	A/ G	0.05128	0.1774	581	5710	1.6472	2.27E-06	0.1071	0.08376	0.1285	56.72	STL

CHR; Chromosome, SNP; single nucleotide polymorphism, BP; base pair, A1; A1 allele, A2; A2 allele, MAF; minor allele frequency, OR; odds ratio, P; P-value, Fq; frequency, AA; African American, EA; European American, Q; p-value for Cochrane's Q statistic, I; I2 heterogeneity index (0-100)