

# Mixed-model Genome-wide Association Analysis of Sleep Duration in a Japanese Large Cohort

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**Abstract** — Though there have been several GWAS of sleep duration, a small number of loci were replicated for the association with sleep duration such as PAX8, CBWD2 and VPK2. Therefore, we conducted a GWAS of sleep duration using a large Japanese cohort. In our linear mixed-model analysis of sleep duration, any loci have neither reached genome-wide significance presumably due to limitations in sample size. Considering that only two loci were discovered in a large-scale GWAS of sleep duration in 128,266 individuals, a GWAS or GWAS meta-analysis using more sample size will need to find further associated variants with sleep duration.

**Keyword:** *Linear Mixed-model; genome-wide association study*

## 1 Introduction

Usual sleep duration is heritable with heritability estimates being around 40%. Candidate gene association studies for sleep duration identified a number of potential loci, though the results were inconsistent. A GWAS of sleep duration have identified and replicated two SNPs near PAX8 and CBWD2 (Gottlieb *et al.*, 2015). Recently, a large-scale GWAS using the UK biobank replicated association with PAX8 and identified new loci, VPK2, and confirmed the association with VPK2 in other samples (Jones SE *et al.*, 2016). However, the identified variants only account for a small amount of the variation in sleep duration. Therefore, we conducted a GWAS of sleep duration using data from the Japan Multi-Institutional Collaborative Cohort Study (J-MICC study) using a linear mixed-model (LMM).

## 2 Methods

### 2.1 Sample

The J-MICC study is one of the largest population-based cohort studies in Japan. The participants were enrolled in 10 study areas throughout Japan except for the northern region. Phenotype information was obtained from self-administered questionnaires at study entry. The ethics committees of all participating institutions approved the protocol for the J-MICC study, and all participants provided written informed consent. Genotyping was performed with the Illumina Infinium OmniExpressExome-8 BeadChip. In total, 513,776 SNPs in 14,088 participants passed our quality control criteria (MAF% ≥ 1%, HWE p-value ≥ 0.001 and call rate ≥ 95% for both individuals and markers).

### 2.2 Analysis

To perform LMM analysis of sleep duration adjusted for age and gender we used BOLT-LMM (Lohet *et al.*, 2015). BOLT-LMM reported no improvement of the non-infinitesimal mixed model test over the standard infinitesimal test and thus we report the results based on the latter.

## 3 Results

Any loci have neither reached genome-wide significance (Table 1 and Figure 1).

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Table 1: Results for the Top 10 SNPs

SNP	Chromosome	Beta	P-value
exm-rs12229654	12	-0.08	1.30E-07
exm329750	3	5.09	2.20E-07
rs2188380	12	-0.08	2.20E-07
rs13153325	5	0.07	3.40E-07
rs4764852	12	-0.06	9.90E-07
exm313929	3	4.76	1.30E-06
exm792711	9	4.76	1.30E-06
rs197146	19	4.76	1.30E-06
rs11874550	18	0.08	4.70E-06
rs6028312	20	0.06	5.20E-06

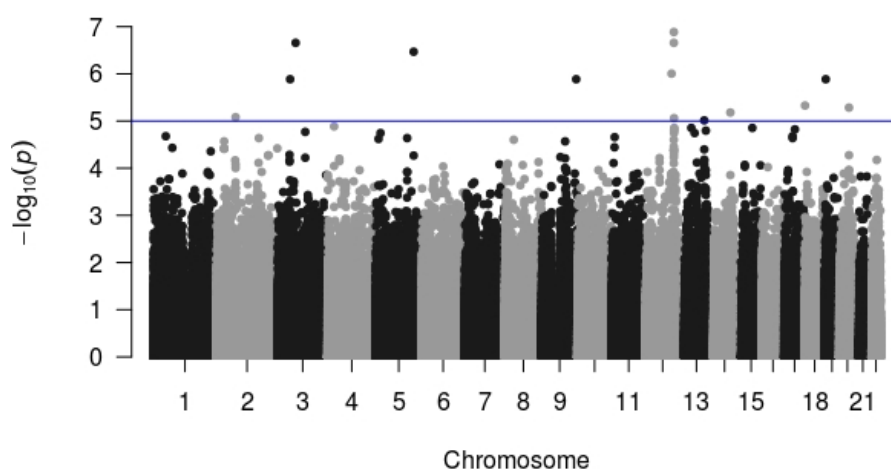


Figure 1: Manhattan Plot

#### 4 Discussions and summary

We performed a GWAS of sleep duration in 14,088 individuals from the JMICC study but we could not find any genome-wide significant signals. Considering that only two loci were discovered in a large-scale GWAS of sleep duration in 128,266 individuals, this non-significant finding is presumably due to limitations in sample size. A GWAS or GWAS meta-analysis using more sample size will need to find further associated variants with sleep duration.

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