Higher polygenic risk for insomnia is associated with lower delta power during habitual sleep in young individuals without sleep disorders

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Background

Insomnia is the most common sleep disorder. Yet, its treatment remains difficult. A full understanding of the factors contributing to insomnia is therefore crucial to design novel efficient strategies. Here, we assessed whether genome-wide polygenic risk score (PRS) for insomnia is associated with sleep in young healthy adults devoid of any sleep complaints.

Methods

Goal: to see if the genetic liability for insomnia is associated with EEG and non-EEG sleep metrics in young healthy individuals

- **Sleep metrics were extracted from EEG sleep recordings, actimetry and questionnaires**
- **Genetic liability was represented by polygenic risk score (PRS). 11 PRSs for each individual were computed based on the 23andMe summary statistics (N=944.477) for insomnia.**

GLM statistical analyses were applied to see if any of the PRSs are associated with any of the sleep metrics.

Participants and protocols

- **N = 456**
- **Age:** 18-31 (22 ± 2.68)
- **Females 49, males 407**
- **Caucasian**
- **Healthy**
- **Exclusion criteria** were the same for all the studies: BMI > 29; excessive alcohol and coffee consumption, psychiatric history, shift work in the past year, transmeridian travel in the last 3 months, sleep apnea, taking sleep medication.
- **Protocols** of the studies were different, but all of them contained a **baseline night** of sleep starting at habitual sleep time and lasting for ~ 8 hours for most but an 8h regular sleep schedule was imposed to part of them

Sleep metrics:

- Wake after sleep onset (**WASO**)
- Sleep onset latency (**SOL**) to N2 stage of sleep
- Rapid eye movement (**REM**) sleep duration
- Total sleep time (**TST**) as a covariate
- **N3 and/or N2 duration** for exploration
- Slow wave energy (**SWE**) accumulated power in the lower frequency range (0.5 - 4 Hz) during non-REM sleep
- Accumulated **beta power** (16.25 - 25 Hz) during non-REM sleep
- **Number of arousals** (during REM and non-REM sleep) (Coppieters 't Wallant et al., 2016)
- SWE during the first hour for exploration
- SWA decrease time constant and SWA_intercept following exponential fit for exploration

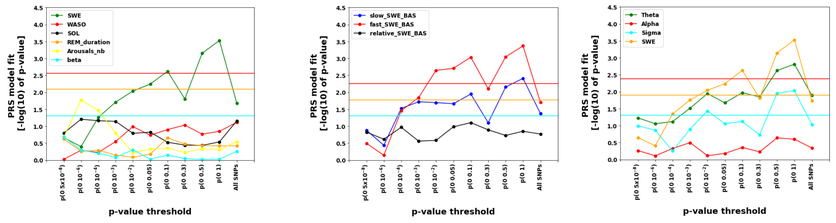
Working with genetic data: quality control, imputation, clumping and computing PRS

The genotyping was performed using the Illumina Infinium BeadChip arrays.
Quality control of the data: PLINK software (http://zzz.bwh.harvard.edu/plink/) (Purcell et al., 2007)
Imputation: Sanger imputation server (https://imputation.sanger.ac.uk/)
Clumping (PLINK)
P-value thresholding: by applying a p-value threshold, i.e., using only markers that achieve a given significance threshold for association between the SNP and the disease (insomnia or depression) (p-value < 5*10^-8, 10^-6, 10^-4, 0.001, 0.01, 0.05, 0.1, 0.3, 0.5, and 1), we computed 10 PRSs for each individual, using **23andMe** data. We then computed the 11th PRS by taking all the SNPs from the summary statistics, without clumping.
We obtained therefore **11 PRSs** for each individual for each of the disease, insomnia and depression.

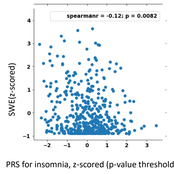
Conclusion

These results show that slow wave sleep intensity can be associated with insomnia liability in healthy young individuals without sleep disorders. They suggest that individual ability or need to generate slow waves during sleep is related to the risk of developing insomnia. The low power in slow waves could be interpreted as a marker of altered sleep homeostasis that had been previously suggested as a contributing factor for insomnia.

Results



Statistical outcomes of GLMs with six sleep metrics of interest vs. insomnia PRS from conservative (p < 5x10-8) p-value threshold to using all SNPs. GLMs are corrected for age, gender, BMI and total sleep time (TST).
Negative log transformation of p-values of the associations are presented on the vertical axis.
The horizontal lines indicate different p-values thresholds: cyan = .05 (uncorrected); orange = .008 (corrected for 6 sleep metrics); red = 0.0028 (experiment-wise correction)



PRS for insomnia, z-scored (p-value threshold = 1)

Lower SWE is associated with higher insomnia liability

	p-value threshold										
Sleep metrics	p=5x10^-8	p =10^-6	p =10^-4	p=0.001	p=0.01	p=0.05	p=0.1	p=0.3	p=0.5	p=1	All SNPs
SWE	NS			β = -0.11 p = 0.02	β = -0.12 p = 0.01	β = -0.12 p = 0.01	**β = -0.14 p = 0.002***	β = -0.11 p = 0.02	**β = -0.15 p = 0.001***	**β = -0.16 p = 0.0003***	β = -0.11 p = 0.02*
WASO	NS										
SOL	NS										
REM_duration	NS										
Arousals_nβ	NS	β = 0.1 p = 0.02	β = 0.09 p = 0.03	NS							
Beta_power	NS										

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