

Genome-wide association meta-analysis and Mendelian randomization analysis confirm the influence of *ALDH2* on sleep duration in the Japanese population

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Sleep, Volume 42, Issue 6, June 2019, zsz046, <https://doi.org/10.1093/sleep/zsz046>

Published: 22 February 2019 [Article history](#) ▼

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Abstract

Usual sleep duration has substantial heritability and is associated with various physical and psychiatric conditions as well as mortality. However, for its genetic locus, only *PAX8* and *VRK2* have been replicated in previous genome-wide association studies (GWAS). We conducted a GWAS meta-analysis of self-reported usual sleep duration using three population-based cohorts totaling 31 230 Japanese individuals. A genome-wide significant locus was identified at 12q24 (p -value $< 5.0 \times 10^{-8}$). Subsequently, a functional variant in the *ALDH2* locus, rs671, was replicated in an independent sample of 5140 Japanese individuals (p -value = 0.004). The association signal, however, disappeared after adjusting for alcohol consumption, indicating the possibility that the rs671 genotype modifies sleep duration via alcohol consumption. This hypothesis explained a modest genetic correlation observed between sleep duration and alcohol consumption ($r_G = 0.23$). A Mendelian randomization analysis using rs671 and other variants as instrumental variables confirmed this by showing a causal effect of alcohol consumption, but not of coffee consumption on sleep duration. Another genome-wide significant locus was identified at 5q33 after adjusting for drinking frequency. However, this locus was not replicated, nor was the *PAX8* and *VRK2*. Our study has confirmed that a functional *ALDH2* variant, rs671, most strongly influences on usual sleep duration possibly via alcohol consumption in the Japanese population, and presumably in East Asian populations. This highlights the importance of considering the involvement of alcohol consumption in future GWAS of usual sleep duration, even in non-East Asian populations, where rs671 is monomorphic.

[usual sleep duration](#), [alcohol consumption](#), [genome-wide association study](#), [Mendelian randomization](#)

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