GWAS of 89,283 individuals identifies genetic variants associated with being a morning person

Youna Hu1, Alena Shmygelska1, David Tran1,2, Nick Eriksson1, Joyce Tung1, David Hinds1
123andMe, Inc, Mountain View, CA, 94043
2Department of Biological Sciences, San Jose State University, San Jose, CA, 95112

Abstract
Circadian rhythms are a nearly universal feature of living organisms and affect almost every aspect of biology. Our innate preference for mornings or evenings is determined by the phase of our circadian rhythms. We conducted a genome-wide association analysis of self-reported morningness, following up analyses of biological pathways and related phenotypes. We identified 15 significantly associated loci, including 7 near established circadian genes. Both circadian and phototransduction pathways are enriched in our results. Morningness is associated with many sleep phenotypes such as insomnia and sleep duration. Morningness is also associated with body mass index and depression but we did not find evidence for a causal relationship. Our findings reinforce current understanding of circadian biology and will guide future studies of circadian rhythms, sleep and related disorders.

Introduction
A morning person prefers to rise and rest early, whereas an evening person would choose a cycle later in the day. Chronotype is the study of such differences. It is
• initially proposed by Kleitman1
• often assessed by the Horne and Ostberg questionnaire
• governed by circadian rhythm, mediated by suprachiasmatic nucleus (SCN)

Genetics studies of circadian rhythms are typically conducted on model organisms.
• The first circadian clock genes were per in Drosophila2 and CLOCK in mice3
• Human linkage studies implicated PER2 in familial advanced sleep phase syndrome4
• Candidate gene studies have found others but study sizes have been small and findings are not robust
• No significant genes have been reported by genome-wide association studies (GWAS)

Methods
23andMe cohort
All participants were drawn from the customer base of 23andMe, Inc., a personal genetics company. Participants were genotyped on one of the three illumina-based BeadChips. We collected phenotypes by inviting participants to login in our website to answer surveys. Our morning person phenotype definition is from combining the answers to two questions that ask if the participant is naturally a night person or morning person.

GWAS analysis
We conducted a GWAS of self-reported morningness in the 23andMe participant cohort across a total of 8 million genotyped or imputed polymorphic sites. We only included samples of European ancestry and no pair was more closely related than at the level of first cousin.

Pathway analysis
We downloaded a database of canonical pathways of 1,320 biologically defined gene sets, then used gene set enrichment analysis (GSEA)5, implemented in MAGENTA6 on our morningness GWAS results.

Morningness and other phenotypes
Depends on the continuity or discreteness of phenotypes, we used logistic or linear regression to estimate the effect of morningness after adjusting for age, sex and top five PCs. We calculated a morning person genetic risk using significant SNPs close to genes with well-known circadian role and carried out a Mendelian randomization (MR) analysis to evaluate the causal role of morningness. Similarly, we calculated a BMI genetic risk to assess possible reverse causality.

Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Marker</th>
<th>Chr</th>
<th>Position</th>
<th>SNP quality</th>
<th>AEs &amp; (A/B)</th>
<th>EAF</th>
<th>OR</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>RGS16</td>
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<td>0.69</td>
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</tbody>
</table>

Genes with well-known circadian role

GWAS analysis
The effect of morningness on sleep phenotypes, BMI and depression. For binary phenotypes, we reported odds ratio (OR) and used (P < 10-5) and (P < 10-1) to denote significance levels.

Acknowledgments
We thank the customers of 23andMe for participating in this research and the employees of 23andMe for their contributions to this work.

Discussion
• We identified many genetic loci associated with morningness but not other related sleep phenotypes such as insomnia, sleep apnea, possibly due to their genetic heterogeneity or our limited sample size of cases.
• Our MR analysis suggests a lack of statistical evidence of the causal relationship between morningness and BMI or depression. Instead, their observed association may reflect effects of other factors such as environment, socioeconomic status, personality or other genetic variables through independent mechanisms.

References
1. Kleitman, N. Sleep and wakefulness as alternating phases in the cycle of existence. xi, 638 p. (Univ. of Chicago Press, 1939).

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