

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



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Abstract

Circadian rhythms are a nearly universal feature of living organisms and affect almost every biological process. 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, followed by 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 Ostberg² 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 *Drosophila*³ and *CLOCK* in mice⁴
- Human linkage studies implicated *PER2* in familial advanced sleep phase syndrome⁵
- 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)⁶, implemented in MAGENTA⁷ 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

Demographic characteristics of the GWAS cohort

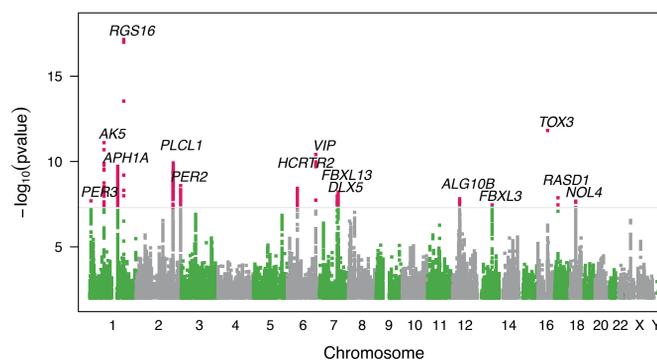
	Morning persons N (% of total)	Evening persons N (% of total)	Proportion that are morning persons
Total	38,937 (100.0%)	50,346 (100.0%)	43.6%
Sex			
Male	19,569 (50.3%)	29,713 (59.0%)	39.7%
Female	19,368 (49.7%)	20,633 (41.0%)	48.4%
Age			
< 30	3,684 (9.5%)	11,521 (22.9%)	24.2%
30–45	8,809 (22.6%)	19,470 (38.7%)	31.2%
45–60	12,295 (31.6%)	11,111 (22.1%)	52.5%
>60	14,149 (36.3%)	8,244 (16.4%)	63.1%

Results

Index significant SNPs that are associated with being a morning person

Gene	Marker	Chr	Position	SNP quality	Alleles (A/B)	BAF	OR	P value
Genes with well-known circadian role								
<i>RGS16</i>	rs12736689	1	182549729	0.97	C/T	0.97	0.74	7.0x10 ⁻¹⁸
<i>VIP</i>	rs9479402	6	153135339	0.85	C/T	0.99	0.69	3.9x10 ⁻¹¹
<i>PER2</i>	rs55694368	2	239317692	0.66	G/T	0.07	0.86	2.6x10 ⁻⁹
<i>HCRTR2</i>	rs35833281	6	55021561	0.99	C/G	0.79	0.92	3.7x10 ⁻⁹
<i>RASD1</i>	rs11545787	17	17398278	0.88	A/G	0.76	1.08	1.4x10 ⁻⁸
<i>PER3</i>	rs11121022	1	7836659	0.98	A/C	0.42	1.07	2.0x10 ⁻⁸
<i>FBXL3</i>	rs9565309	13	77577027	>0.99	C/T	0.97	1.19	3.5x10 ⁻⁸
Genes with plausible circadian role								
<i>PLCL1</i>	rs1595824	2	198874006	>0.99	C/T	0.49	1.08	1.2x10 ⁻¹⁰
<i>APH1A</i>	rs34714364	1	150234657	0.64	G/T	0.17	1.12	2.0x10 ⁻¹⁰
<i>FBXL13</i>	rs3972456	7	102436907	0.66	A/G	0.71	0.92	6.0x10 ⁻⁹
<i>NOL4</i>	rs12965577	18	31675680	>0.99	A/G	0.34	0.94	2.1x10 ⁻⁸
Genes with less clear circadian role								
<i>TOX3</i>	rs12927162	16	52684916	0.96	A/G	0.26	0.91	1.6x10 ⁻¹²
<i>AK5</i>	rs10493596	1	77726241	>0.99	C/T	0.24	1.09	8.0x10 ⁻¹²
<i>DLX5</i>	rs2948276	7	96457119	0.99	A/G	0.18	0.92	1.1x10 ⁻⁸
<i>ALG10B</i>	rs6582618	12	38726137	0.92	A/G	0.52	1.07	1.5x10 ⁻⁸

Manhattan plot of the GWAS of being a morning person



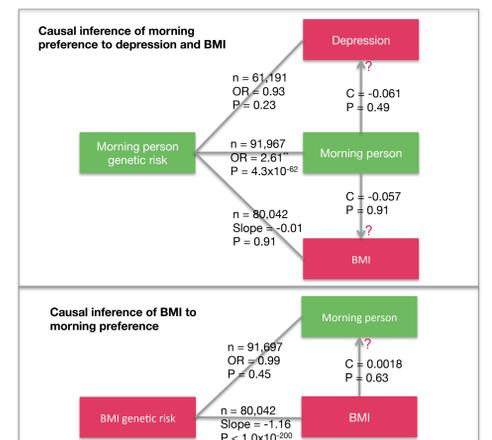
Top pathways analyzed by MAGENTA⁷

1. KEGG circadian rhythm	• # of genes: 13 • Gene set p value: 2.0x10 ⁻⁴ • FDR = 0.059
2. REACTOME circadian clock	• # of genes: 53 • Gene set p value: 4.0x10 ⁻⁴ • FDR = 0.20
3. REACTOME BMAL1, CLOCK, NPAS2 activates circadian expression	• # of genes: 36 • Gene set p value: 1.9x10 ⁻³ • FDR = 0.42
4. REACTOME Tetrahydrobiopterin BH4 synthesis recycling salvage and regulation	• # of genes: 13 • Gene set p value: 3.1x10 ⁻³ • FDR = 0.22
5. REACTOME phospholipase C-beta mediated events	• # of genes: 43 • Gene set p value: 4.3x10 ⁻³ • FDR = 0.52

Morningness and other phenotypes



The effect of morningness on sleep phenotypes, BMI and depression. For binary phenotypes, we reported odds ratio in the parentheses; for continuous BMI, we reported slope and used * ($P < 10^{-5}$) and ** ($P < 10^{-14}$) to denote significance levels.



Visualization of MR result. The lines without arrows between two phenotypes denote the associations. We reported sample size (n), effect size (odds ratio (OR) or slope) and P value. The arrowed lines describe the causal inference of two phenotypes. We reported the causal effect (C) and P value.

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, socioeconomics, personality or other genetic variables through independent mechanisms.

References

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