Genetic Architecture of Chronotype

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Background

Chronotype (early morning vs. evening) describes an person natural tendency to fall asleep and wake up at earlier or later time.

Chronotype has been associated with a range of health and performance outcomes, including sleep disorders, cognitive and physical performance deficits.

> Nat Commun. 2019 Jan 29;10(1):343. doi: 10.1038/s41467-018-08259-7.

Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms

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Abstract

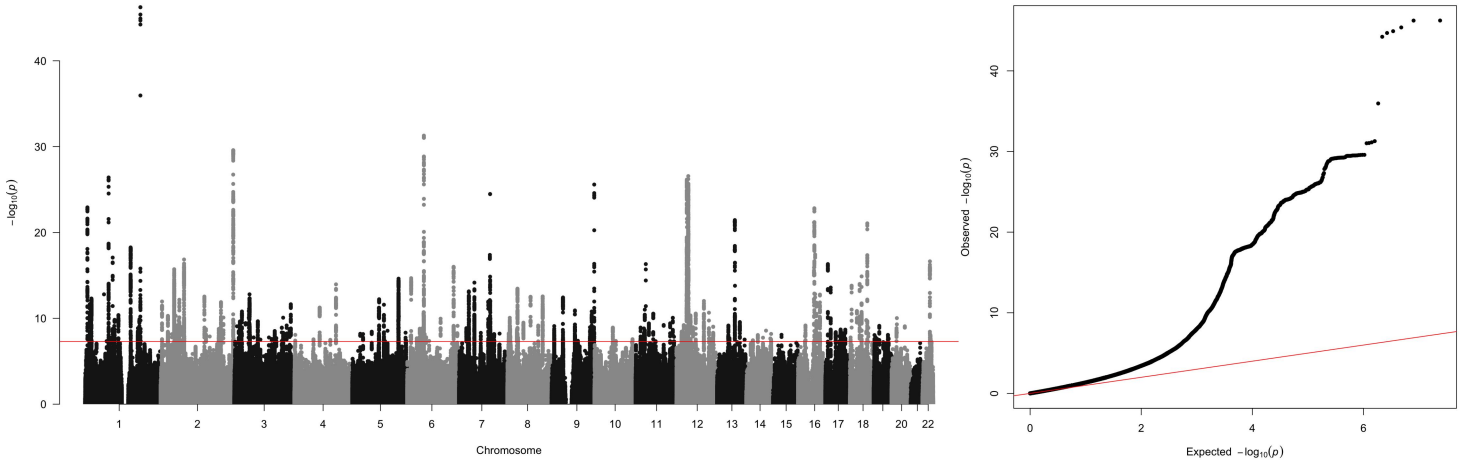
Being a morning person is a behavioural indicator of a person's underlying circadian rhythm. Using genome-wide data from 697,828 UK Biobank and 23andMe participants we increase the number of genetic loci associated with being a morning person from 24 to 351. Using data from 85,760 individuals with activity-monitor derived measures of sleep timing we find that the chronotype loci associate with sleep timing: the mean sleep timing of the 5% of individuals carrying the most morningness alleles is 25 min earlier than the 5% carrying the fewest. The loci are enriched for genes involved in circadian regulation, cAMP, glutamate and insulin signalling pathways, and those expressed in the retina, hindbrain, hypothalamus, and pituitary. Using Mendelian Randomisation, we show that being a morning person is causally associated with better mental health but does not affect BMI or risk of Type 2 diabetes. This study offers insights into circadian biology and its links to disease in humans.

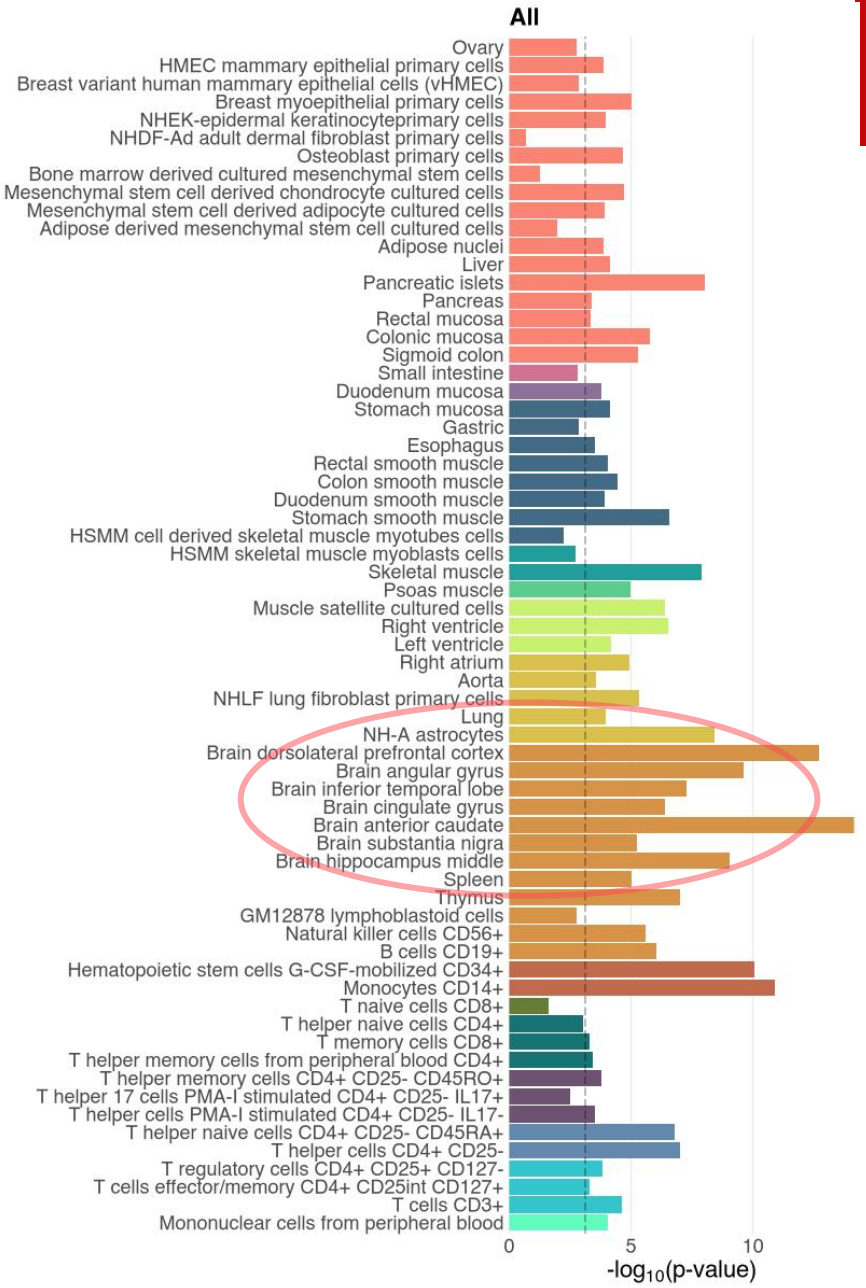
https://pubmed.ncbi.nlm.nih.gov/30696823/

Methods

1. GWAS
2. LD Score Regression
3. Enrichment Plot
4. Genetic Correlation
5. TWAS
5. Mendelian Randomization

GWAS and LDSC:





Several peaks were found with very significant SNPs

LDSC: $h^2 = 0.114$, $p = 0.004$

Enrichment analysis: Strongest in brain tissues, especially the **caudate basal ganglia** and **frontal cortex**. It will be our TWAS direction **afterward!**

LocusZoom

LocusZoom showed the nearest genes to the top SNPs.

rsID	NearestGene	-log10P
rs509476	RGS16	46.244
rs2653349	HCRTR2	31.284
rs57435966	TRAF3IP1	29.585
rs7313852	AC087897.1	26.569
rs7547493	AK5	26.409
rs13377754	RNU6-472P	26.161
rs28458909	EXD3	25.585
rs4729854	AC105052.5	24.481
rs61773390	PER3, Z98884.1	22.921

1. RGS16

RGS16 has been shown to be a key factor in the centre for circadian rhythm control in humans.

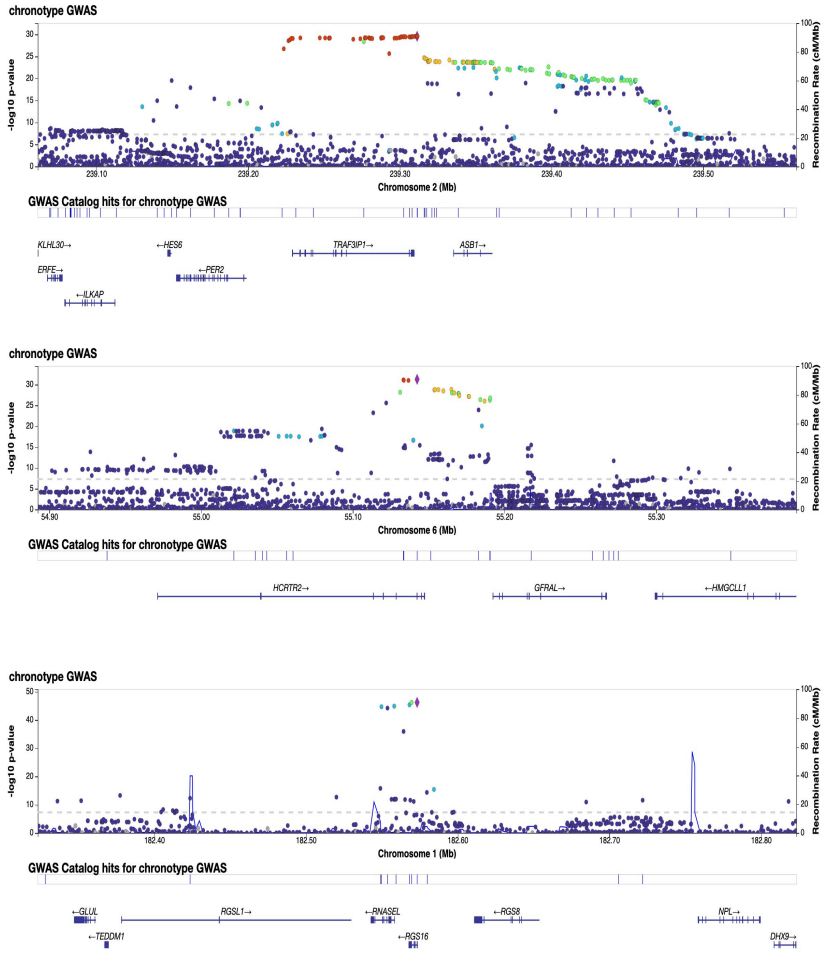
2. HCRTR2

HCRTR2 shows strong linkage disequilibrium (LD, r^2>0.8) with the lead variant, suggesting it may jointly influence circadian clock function.

3. PER3

While mPer3 knockout mice maintained essentially normal locomotor rhythms, their circadian period was significantly shortened by 0.5 hours.

Source: Genome–Wide Association Analyses in 128,266 Individuals Identifies New Morningness and Sleep Duration Loci, Targeted disruption of the mPer3 gene: subtle effects on circadian clock function, GWAS Findings for Human Iris Patterns: Associations with Variants in Genes that Influence Normal Neuronal Pattern Development.



https://my.locuszoom.org/gwas/829813/

TWAS in Brain Tissues

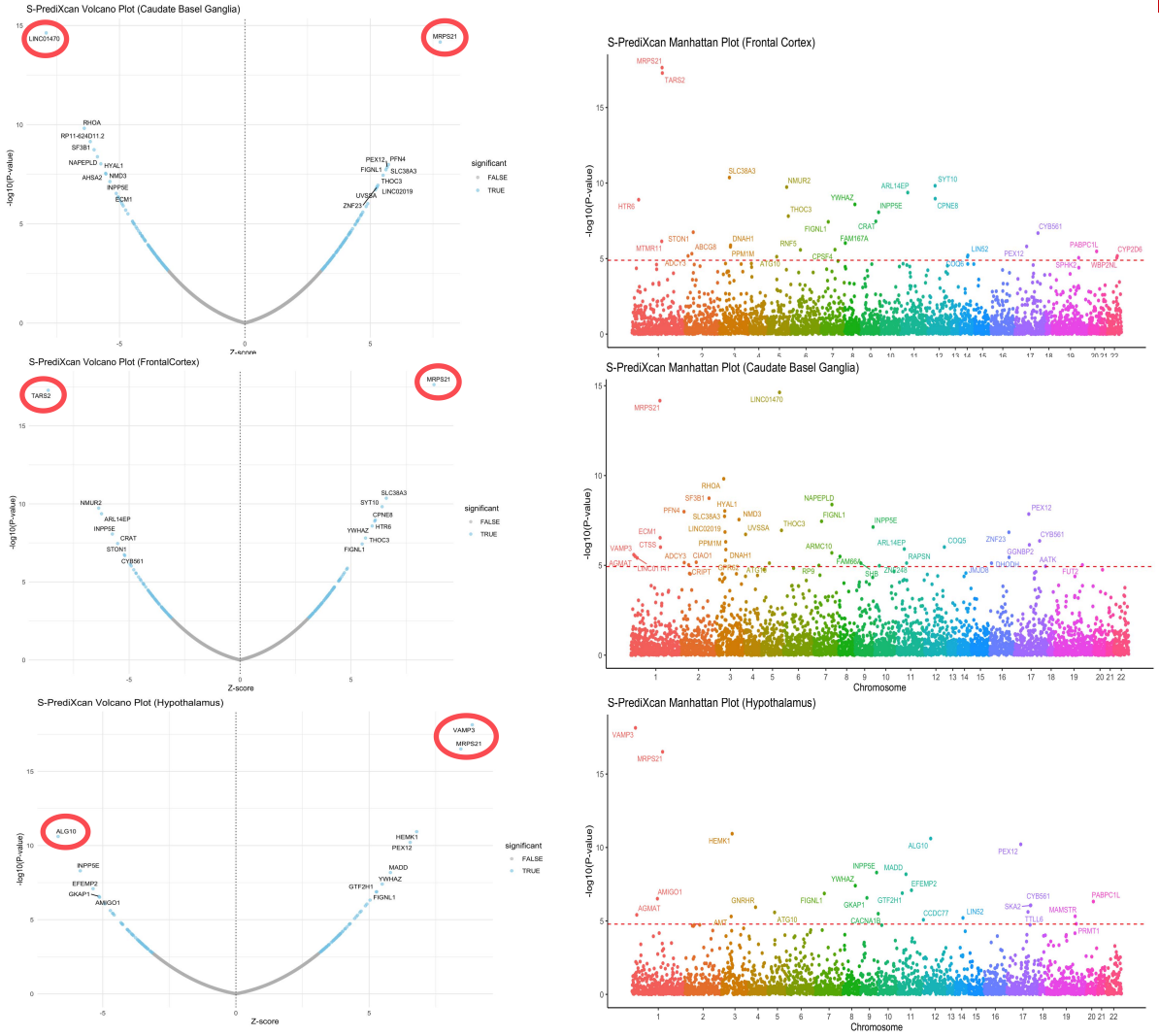
We chose **caudate basel ganglia**, **frontal Cortex** and **hypothalamus** for TWAS.

These are the significantly genes we found by TWAS:

Tissue	Genes
Caudate Basel Ganglia	LINC01470, RHOA, SF3B1, HYAL1, NAPEPLD, MRPS21, ECM1, THOC3, SLC38A3, etc.
Frontal Cortex	TARS2, NMUR2, INPP5E, ARL14EP, HTR6, YWHAZ, THOC3, SLC38A3, MRPS21, etc.
Hypothalamus	ALG10, INPP5E, VAMP3, MADD, YWHAZ, PEX12, MRPS21, etc.

However, these genes have limited reported functional associations with chronotype. Among them, only INPP5E has been linked to chronotype.

MRPS21 ?



Genes with name (FDR < 0.0001), other blue dots(FDR < 0.05)

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We also looked for papers:

1. ARL14EP: Links between daytime light exposure and chronotype expression in modern humans have also been suggested on candidate gene ARL14EP

Source: Exploring adaptive introgression in modern human circadian rhythm genes

2. HTR6: The study identified genetic variants associated with chronotype located near this gene.

Source: Genome–Wide Association Analyses in 128,266 Individuals Identifies New Morningness and Sleep Duration Loci

Genetic correlation

We also did a **correlation anysis** between Chronotype and ADHD, Baldness, EA, napping and SCZ. (Other paper also shows these traits)

It shows eveningness is genetically associated with lower **educational attainment**, lower risk of **schizophrenia** and increased tendency to **nap** during the day.

We found genetic correlation, but it is only correlation.

We want to know causal relationship.

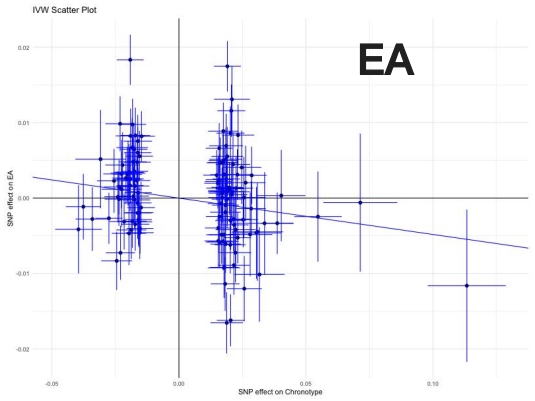
Trait1	Trait2	rg	rg_se	z	p
Chronotype	ADHD	0.0093	0.0248	0.3742	0.7083
Chronotype	**EA**	**-0.1359**	**0.0164**	**-8.278**	**1.2522E-16**
Chronotype	Baldness	0.0057	0.0166	0.3464	0.729
Chronotype	**SCZ**	**-0.1065**	**0.0191**	**-5.5643**	**2.6315E-08**
Chronotype	**Napping**	**0.121**	**0.0218**	**5.5541**	**2.7902E-08**

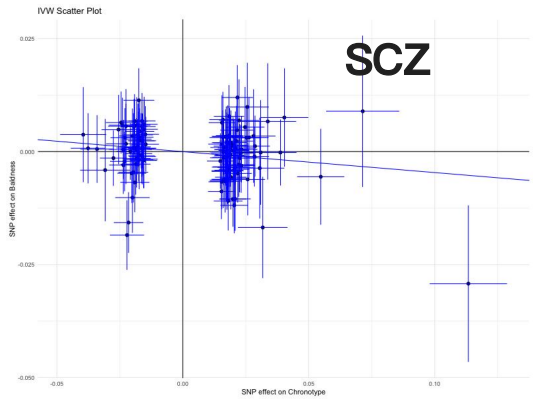
Mendelian Randomization

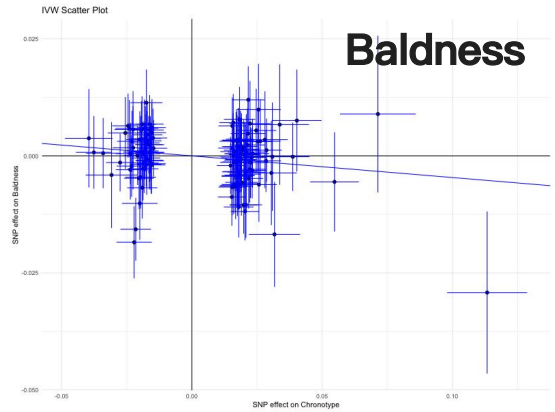
Chronotype → EA – IVW Result
Number of SNPs: 129
Estimate: −0.04822787
Std. Error: 0.02437295
P−value: 0.04784461
Heterogeneity Q: 1150.596
Heterogeneity p: 5.990395e−164
F−statistic: 47.15542

Chronotype → SCZ – IVW Result
Number of SNPs: 129
Estimate: −0.1903335
Std. Error: 0.0890843
P−value: 0.03263422
Heterogeneity Q: 483.0183
Heterogeneity p: 1.180114e−42
F−statistic: 47.15542

Chronotype → Baldness – IVW Result
Number of SNPs: 126
Estimate: −0.04634002
Std. Error: 0.02180374
P−value: 0.03355955
Heterogeneity Q: 270.2007
Heterogeneity p: 1.047867e−12
F−statistic: 47.26016







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Future Work: Our findings regarding the genetic correlation estimates of chronotype exhibit discrepancies when compared with the results reported in the study Genome–wide association analysis identifies novel loci for chronotype in 100,420 individuals from the UK Biobank. Further investigation is required to identify the underlying causes of these inconsistencies.

Thank you

Q & A