Absence of morningness alleles in non-European populations

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Abstract

In spite of suspected circadian differences between different ancestral groups, most human studies have used individuals of European descent. This also applies to three recent genome-wide association studies (GWAS), which pinpointed a number of chronotype loci. We investigated the distribution of these hits in different 1000 Genomes populations. We found six out of the 41 alleles previously identified by GWAS in European participants (in the genes *RGS16*, *PER2*, *AK5*, and between the genes *APH1A* and *CA14*) to be absent from some non-European population groups. This highlights the need for ancestral diversity in circadian research, and may reflect differences affecting the phenotype of individuals of East Asian ancestry.

Keywords

Chronotype; Circadian rhythms; Diurnal preference; Genetics Genome-wide association studies

Introduction

The vast majority of published observations on circadian rhythms and sleep in humans have been made on individuals of European descent. There is reason to assume that there are specific differences in these phenotypes relating to ancestry, given the differences in photoperiod experienced by populations adapted to different latitudes (von Schantz, 2017). Exploring and understanding such differences is a recognised research imperative, as the health disparities observed between different ancestral groups in many societies dictates a need to disentable the socioeconomic and biological components of such disparities (Egan, Knutson et al., 2017) (Prasad, Saxena et al., 2018), so that prevention, diagnosis, and

treatments are not exclusively based on what may be specific biological peculiarities of groups of European ancestries. Chronotype or diurnal preference is a construct that is assessed through questionnaires of varying complexity and sophistication, ranging from 19 questions to a single one (Adan, Archer et al., 2012). At least when based on the more sophisticated measures, such as the morningness-eveningness questionnaire (Horne & Östberg, 1976), chronotype has been shown to correlate with objective measures of circadian period (Duffy, Rimmer et al., 2001). Genetic association studies of chronotype were initially restricted to candidate genes studies (reviewed in (von Schantz, 2017)). The emergence of genome-wide association studies (GWAS) and the availability of measures on chronotype (assessed based on a single question) from public (UK Biobank) and commercial (23andMe) sources recently enabled the publication of the first three GWAS studies on chronotype to yield significant findings (Jones, Tyrrell et al., 2016) (Lane, Vlasac et al., 2016) (Hu, Shmygelska et al., 2016), which were systematically reviewed and summarised in (Kalmbach, Schneider et al., 2017). Reassuringly, and in contrast to many other GWAS studies, a number of the associations reported in these studies agreed with previous candidate gene reports. However, in order to increase sample homogeneity, all of these studies were restricted to individuals of European ancestry, who represented the majority component of both the UK Biobank and the 23andMe samples. Given that there are reports of variability in chronotype between ethnic Europeans and other groups (Eastman, Tomaka et al., 2016) (Egan, Campos Santos et al., 2017) (Malone, Patterson et al., 2017), it becomes important to ascertain to which degree these newly identified chronotype alleles are shared between groups of different ancestry. As an initial step, we have investigated the prevalence of the alleles identified in the three recent GWAS papers in different population, using publically available population data from the 1,000 Genomes project.

Materials and methods

We systematically interrogated superpopulation groups of the 1,000 Genomes database via the NCBI interface for the frequencies all 41 SNPs reported to associate with chronotype in at least one of the three published studies (Jones, Tyrrell et al., 2016) (Lane, Vlasac et al., 2016) (Hu, Shmygelska et al., 2016). Any allele frequencies below 0.01 observed in superpopulations were further explored in constituent populations using the Phase3 browser (Ensembl). Ancestral alleles were identified via Ensembl.

Results and Discussion

We found six out of the 41 alleles previously identified by GWAS in European participants to be absent from some non-European population groups. Examination of the odds ratio for each allele showed that, in all these instances, the allele missing from some populations was the one associated with morningness. The frequencies of these alleles across populations are shown in Table 1. Where there was an allele frequency of below 0.01 in a superpopulation, the distributions in individual constituent populations are shown.

Our confirmation that the majority of the chronotype alleles identified from GWAS studies in participants of European ancestry are shared between all populations does not mean that they necessarily have the same effects in all of them.

Five out of the six morningness alleles reported here were absent from all East Asian reference populations. The sixth one (rs76681500, in the *AK5* gene) was found with a frequency of 0.001 in Kinh in Ho Chi Minh City (Vietnam) (KHV), a population with a complex admixed origin. The three morningness alleles in the *RGS16* were represented in all African populations, but the three others (all in different genes) were absent from most of them. Two of them (rs35333999, in *PER2*, and rs76681500, in *AK5*) were only present in populations with known European and Amerindian admixture (ACB, African Caribbeans from Barbados and, in the case of the latter allele, also in ASW, African Ancestry in Southwest US).

Interestingly, the third (rs34714364, between the *APH1A* and *CA14* genes) was also represented at higher than trace levels (0.010) in LWK (Luhya in Webuye, Kenya). This seems to suggest that the two former were probably derived after the exodus of some groups of our species from Africa, but that the latter may have predated it.

In the subpopulation analysis within the South Asian superpopulation of morningness alleles that were entirely absent from East Asians, all four were found to also be absent from the Sri Lankan Tamil in the UK (STU), and one of them, (rs35333999) from all constituent populations other than Indian Telugu in the UK (ITU).

The only one of the genes implicated in this study as lacking morningness alllele in certain populations which has a clearly defined function in circadian function is *PER2*, and even in this case, there is evidence for a degree of functional redundancy between *PER2* and *PER1* (Bae et al., 2001). Thus, it would be difficult to speculate of the functional consequences of the absence of these alleles based on gene ontology.

Generally, our findings showed that six of the morningness alleles identified by GWAS were absent from specific non-European populations. Three of these were alleles from the same locus (*RSG16*), where the eveningness alleles are combined in a haplotype in all East Asian populations and in Sri Lankan Tamils. The specific absence of morningness, rather than eveningness alleles is striking. Whilst we found no signatures of significant selection around these loci, the morningness alleles may convey advantages to populations living with longer photoperiods. It is not known whether these alleles convey difference in circadian properties in these populations, and nor is enough known about what such differences exist. However, these findings, together with the suggestions of ancestrally determined phenotypic differences discussed above, provide further evidence of the importance of including participants of non-European ancestry in both genotypic and phenotypic analysis of circadian parameters. Further metaanalyses combining data from the UK Biobank and

23andMe, but still restricted to individuals of European ancestry, are forthcoming. Our findings suggest the need to plan and similar analyses of datasets from other ancestral groups, both by analysing minority groups in current datasets and by collecting novel ones.

Declaration of interest

The authors report no conflicts of interest.

Table 1

The table lists the six morningness alleles identified through chronotype GWAS studies that were absent in some populations. Allele information and frequencies in different populations are shown, with three of the superpopulations broken down into constituent populations where applicable. Abbreviations: EAS = East Asian (subpopulations CDX = Chinese Dai, CHB = Han Chinese, CHS = Southern Han Chinese, JPT = Japanese, KHV = Kinh in Vietnam), EUR = European, AFR = African (subpopulations ACB = African Caribbean, ASW = African Ancestry in Southwest US, ESN = Esan in Nigeria, LWK = Luhya in Kenya, MAG = Mandinka in the Gambia, MSL = Mende in Sierra Leone, YRI = Yoruba in Nigeria), AMR = American, SAS = South Asian (subpopulations: BEB = Bengali, GIH = Gujarati, ITU = Indian Telugu, PJL = Punjabi, STU = Sri Lankan Tamil).

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SNP ID	Reference	Nearest gene(s)	Ancestral allele	Morningness allele	Eveningness allele	Allele frequency in GWAS study	SUPERPOPULATIONS AND POPULATIONS																	
							EAS					EUR	AFR							AMR	SAS				
							CDX	CHB	CHS	JPT	KHV		ACB	ASW	ESN	LWK	MAG	MSL	YRI		BEB	GIH	ITU	PJL	STU
rs12736689	Hu et al., 2016	*RGS16, RNASEL*	T	C	T	0.03	0.000					0.024	0.110							0.023	0.012	0.010	0.005	0.010	0.000
rs1144566	Lane et al., 2016	*RGS16*	C	T	C	0.03	0.000					0.022	0.023							0.014	0.012	0.010	0.005	0.010	0.000
rs516134	Jones et al., 2016	*RGS16*	T	C	T	0.03	0.000					0.024	0.198							0.032	0.012	0.010	0.005	0.010	0.000
rs35333999	Lane et al., 2016	*PER2*	C	T	C	0.043	0.000					0.060	0.021	0.000	0.000	0.000	0.000	0.000	0.000	0.029	0.000	0.000	0.005	0.000	0.000
rs34714364	Hu et al., 2016	*APH1A, CA14*	G	T	G	0.17	0.000					0.156	0.021	0.008	0.000	0.010	0.000	0.000	0.000	0.076	0.055				
rs76681500	Lane et al., 2016	*AK5*	G	A	G	0.16	0.000	0.000	0.000	0.000	0.001	0.145	0.021	0.041	0.000	0.000	0.000	0.000	0.000	0.055	0.025				