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ARTICLE

Genetic-based signatures of the latitudinal differences in chronotype

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ABSTRACT

The natural cycles of night and day, and their length, remain stable in near-equatorial African regions but they vary with latitude and season in Eurasia. This new environmental factor might shape the adaptation of circadian rhythms of Eurasians after the out-of-African dispersal of their African ancestors. To identify the genetic-based signatures of this adaptation, geographic variation in allele frequencies of more than 2300 genetic variants was analyzed using data from 5 African and 11 Eurasian populations of the 1000 Genomes Project. The genetic signatures of latitude-dependent polygenic selection were found more frequently within non-coding DNA regions associated with morningness–eveningness in genome-wide association studies (GWASs) than among polymorphisms hinted by GWASs of other traits/diseases and among polymorphisms sampled from pseudogenes and from protein-coding regions in either circadian clock genes or reference genes. Some of such variants were located within the introgressions of the Neanderthal's genome into the genomes of Eurasians.

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Introduction

The observations of latitudinal differences in chronotype (diurnal preference) were reported for both Northern (Randler 2017) and Southern Hemispheres (Leocadio-Miguel et al. 2017). Such observations suggested an increase in prevalence of eveningness at higher latitudes. This shift might be simply explained by the latitude-dependent reduction of the exposure to light (Leocadio-Miguel et al. 2017). However, given that genetic influences account for, at least, one third of the variance in diurnal preference (Hur et al. 1998; Koskenvuo et al. 2007; Watson et al. 2013), these influences can partly contribute to the reported latitudinal shift in chronotype.

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Moreover, these influences can be also suggested from the reports on significant differences in chronotype between people tracing their ancestry to different continents. In Brazil, a shift toward morning preference was linked to Amerindian rather than to African and European ancestries (Egan et al. 2017). In the USA, a more pronounced morning preference was found in African Americans compared to non-Hispanic European Americans (Eastman et al. 2016; Malone et al. 2017). Moreover, the experimental studies of their circadian rhythms pointed at a shorter circadian period (Eastman et al. 2012, 2016, 2017) and a larger impact of extreme circadian misalignment on sleep duration (Paech et al. 2017). Therefore, it cannot be excluded that latitudinal and racial differences in chronotype were, at least partly, shaped by polygenic latitude-dependent adaptation to seasonal variation in day length at higher latitudes.

In our candidate gene study, we found significant association between diurnal preference and two of seven examined single nucleotide polymorphisms (SNPs) in five circadian clock genes (Dorokhov et al. 2018). The analysis of geographic variation in allele frequencies of these two SNPs on example of 16 (11 Eurasian and 5 African) populations sampled for the 1000 genomes project suggested their significant association with latitude. This association became even stronger after combining frequencies provided by the 1000 genomes project with frequencies obtained for our samples represented different Russian regions (Dorokhov et al. 2018). Then we compared 13 SNPs in 10 circadian clock genes showing significant association with chrontype in the previous candidate gene studies with 13 SNPs in the same genes not showing such an association and found significant difference in favor of the former 13 SNPs in the number of significant correlates of latitude (Putilov et al. 2018). Finally, we analyzed geographic variation in allele frequency of 1665 polymorphisms and found that (1) prevalence of genetic signatures of latitude-dependent selection among polymorphisms in 12 circadian clock genes was higher than among polymorphisms in 12 reference genes, i.e. genes linked to other than chronotype quantitative traits, and that, on the other hand, (2) this prevalence was lower than among polymorphisms in 12 genes underlying skin pigmentation, a quantitative trait with a rather simple genetic architecture, i.e. when fewer genes produce stronger effects (Putilov et al. 2018).

However, it remained unknown how big is the contribution of the latitude-dependent polymorphisms in circadian clock genes to individual variation in diurnal preference. It is now become clear that much of genetic basis of quantitative traits is non-coding, presumably due to a profoundly larger impact of the regulatory rather than protein-coding variants. At least, most peaks yielded by a genome-wide association study (GWAS) map to non-protein-coding DNA sequences (e.g. Grossman et al. 2010). Of 34 loci-significant associates of chronotype yielded by three GWASs (Hu et al. 2016; Jones et al. 2016; Lane et al. 2016; reviewed by Kalmbach et al. (2017)), several loci were located in close proximity to such circadian clock genes as *PER2* and *PER3*, but not within these genes thus pointing at regulatory (non-protein-coding) function of these regions. It is reasonable to expect that, in the case of the vast majority of causal variants within and outside the circadian clock genes, each variant explains just a small amount of variation in chronotype, and, therefore, its effect does not reach a stringent significance threshold of a GWAS study.

A paradoxical prediction can be made from such GWAS findings: genetic signatures of latitude-dependent selection can be less common among polymorphisms mapped in circadian clock genes than among polymorphisms located outside these and any other protein-coding sequences. Consequently, the present analysis was mostly aimed on testing this

prediction. The analysis was additionally aimed on examination of several other predictions concerning the probability of identification of genetic signatures of latitude-dependent selection in the set of 34 polymorphisms collectively yielded by the three GWAS of chronotype (Kalmbach et al. 2017). More specifically, one of the predictions was that, if the signatures of latitude-dependent selection more common among polymorphisms from this set than among polymorphisms sampled from circadian clock genes, even larger differences in favor of the set of the loci-associates of chronotype can be found in comparisons with polymorphisms sampled from reference genes and pseudogenes as well as in comparison with the sets of polymorphisms yielded by GWASs of other traits/diseases. However, the exceptions (i.e. the absence of significant difference) can be also predicted, for instance, for the sets of polymorphisms representing other traits shaped by latitude-dependent adaptations, such as a set of polymorphisms hinted by a GWAS of skin pigmentation or a set of polymorphisms showing the signs of recent positive selection.

Methods

Using the data-set of the 1000 Genomes Project Phase 3 (Sudmant et al. 2015) geographic variation in more than 2300 polymorphisms (SNPs and short indels, i.e. deletions and insertions) was analyzed. Genotype frequencies are available for, in total, 2504 individuals from 26 populations (e.g. http://grch37.ensembl.org/Homo_sapiens/Variation/Sample?r=11:88915070–88916070;v=rs7129973;vdb=variation;vf=4214080#373507_tablePanel). It is a very challenging problem to assign latitude to 10 of these 26 populations due to a rather recent rapid change in a place of population's residence and/or a rather modern origin of population through admixture of people from different continents. Therefore, these 10 samples (910 individuals) were not included in the analyses illustrated in Tables 1–5 and Figures 1–3 (Sri Lankan Tamil and Indian Telugu in the UK, Gujarati Indian in the USA, Puerto Rican in Puerto Rico, African Caribbean in Barbados, Peruvian in Peru, Colombian in Colombia, people of African, Mexican and European ancestry in the USA). Of 16 remaining populations, near equatorial Africa was always the place of residence for five populations (Yoruba and Esan in Nigeria, Luhya in Kenya, Mende in Sierra Leone, and Gambian in Gambia). Eleven other populations have evolved within the continent of Eurasia after the out-of-African exodus of their common ancestral population (Japanese in Tokyo, Han Chinese in Bejing, Southern Han Chinese, Chinese Dai in Xishuangbanna, Kinh in Ho Chi Minh City, Bengali in Bangladesh, Punjabi in Lahore, Toscani in Italy, Iberian in Spain, British in the UK, and Finnish in Finland).

In total, 27 sets of polymorphisms were analyzed (Figure 1 and Tables 1, 2 and 4) to compare these sets with the set representing 34 polymorphisms-associates chronotype that were collectively yielded by three GWASs (Hu et al. 2016; Jones et al. 2016; Lane et al. 2016) and reviewed by Kalmbach et al. (2017). The number of polymorphisms chosen to represent most of other sets was also limited to 34. In particular, 34 most reliable or/and most strongly associated polymorphisms were chosen from the original reports or reviews of GWASs that yielded the associates of type 2 diabetes (Morris et al. 2012), body mass index (BMI; Locke et al. 2015), sleep traits (reviewed by Goel 2017), bipolar disorder (Ikeda et al. 2017), schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014), amyotrophic lateral sclerosis (Schymick et al. 2007) and skin pigmentation (Stokowski et al. 2007). Moreover, from a meta-analysis of such genetic associates of traits/diseases (Hindorff et al. 2009) two sets of 34 SNPs were additionally included in the analysis to represent

Table 1. Fractions of polymorphisms meeting multiple criteria of latitude-related selection.

Multiple criterion		Dual			Triple*			
Single criterion, $p < 0.05$: SD or ρ_{16}		SD,	SD,	ρ_{16},	SD,	χ^2-test		
Single criterion, $p < 0.05$: ρ_{16} or ρ_{11}	*n*	ρ_{16}	ρ_{11}	ρ_{11}	ρ_{16}, ρ_{11}	χ^2	*p*	df
Polymorphisms in circadian clock genes tested as markers of chronotype or sleep times								
Association was found (partly)	7	**0.714**	**0.286**	**0.286**	**0.286**			
Association was found	13	**0.615**	**0.462**	**0.308**	**0.308**	2.23	0.135	1
Association was not found	13	0.077	**0.385**	0.077	0.077			
1665 polymorphisms with MAF > 0.200 selected from 36 genes of three groups								
12 reference genes	537	0.132	**0.216**	0.091	0.037	**59.75**	**<0.001**	**2**
12 circadian clock genes	587	**0.223**	**0.332**	0.128	0.085			
12 skin pigmentation genes	541	**0.294**	**0.329**	**0.218**	0.176			
112 strong correlates of latitude ($-0.8366 < \rho_{16} > 0.8366$) among 1665 polymorphisms								
Among reference genes	15	**0.533**	**0.615**	**0.533**	**0.533**	**9.55**	**0.008**	**2**
Among circadian clock genes	25	**0.800**	**0.800**	**0.960**	**0.800**			
Among skin pigmentation genes	72	**0.917**	**0.889**	**0.958**	**0.875**			
204 reference polymorphisms listed in 6 GWAS studies of associates of traits/diseases								
Associates of type 2 diabetes	34	**0.235**	**0.294**	**0.206**	0.059	2.38	0.794	5
Associates of BMI	34	0.118	**0.353**	0.176	0.059			
Associates of sleep traits	34	0.118	**0.235**	0.118	0.088			
Associates of bipolar disorder	34	0.118	**0.294**	**0.324**	0.088			
Associates of schizophrenia	34	**0.353**	**0.324**	**0.206**	0.147			
Associates of sclerosis	34	**0.235**	**0.265**	**0.206**	0.118			
68 polymorphisms listed in two GWAS studies of associates of latitude-related traits								
Associates of chronotype	34	**0.441**	**0.471**	**0.294**	**0.294**	0	1.000	1
Associates of skin pigmentation	34	**0.441**	**0.588**	**0.294**	**0.294**			
68 polymorphisms from two meta-analyses of associates of traits/diseases								
Associates of two traits/diseases	34	**0.382**	**0.294**	**0.206**	**0.206**	0.09	0.769	1
SNPs under positive selection	34	**0.324**	**0.412**	**0.294**	**0.235**			
272 polymorphisms from 8 pseudogenes								
HMGA1P7	34	0.059	0.029	0	0	**15.06**	**0.035**	**7**
NBPF13P	34	**0.382**	0	0	0			
NBPF22P	34	0.059	0.118	**0.294**	0			
TBC1D3P1-DHX40P1	34	0.088	0.088	0.029	0.029			
COL6A4P2	34	**0.264**	**0.588**	0.059	0.059			
DTX2P1-UPK3BP1-PMS2P11	34	0.118	**0.529**	0.029	0.029			
ANKRD62P1-PARP4P3	34	**0.324**	**0.235**	0.176	0.147			
PTENP1	34	0.088	0.088	0.059	0.059			

Notes: List of polymorphisms in **bold**: Significantly **higher** fraction was expected for this set of polymorphisms. Fraction in **bold**: Fraction is higher than 0.200. Results of χ^2-test in **bold**: Comparison of sets of polymorphisms within a group of sets suggested significant difference between them in fraction of polymorphisms meeting the triple criterion; *Illustrated in Figure 1.

polymorphisms associated simultaneously with two traits/diseases and SNPs showing the signs of recent positive selection (i.e. extended haplotypes due to selective sweeps).

Similarly, a set of 34 polymorphisms was selected from the list of polymorphisms available for each of 8 pseudogenes. Since the polymorphisms of a gene are sorted at their web-page by default order (e.g. https://www.ncbi.nlm.nih.gov/snp?LinkName=gene_snp&from_uid=646300), a selection always started from the last of the listed polymorphisms towards the 1st listed polymorphism to be completed after selection of the 34th polymorphism with Global Minor Allele Frequency (GMAF) >0.01.

Nine other sets from our previous publications (Dorokhov et al. 2018; Putilov et al. 2018) were included in the present analysis (## 1–9) in addition to these 18 sets of polymorphisms

Table 2. Pairwise comparison of fractions of polymorphisms meeting the triple criterion.

Triple criterion ($p < 0.05$: SD, ρ_{16} and ρ_{11})		Met*	**Vs. # 16**		Vs. ## 10–15		Vs. ## 20–27	
#	Set of polymorphisms	Yes-No	χ^2_1	p	χ^2_1	p	χ^2_1	p
1	**Association was found (partly)**	2–5	0.00	0.964	2.80	0.094	**9.24**	**0.002**
2	**Association was found**	4–9	0.01	0.928	5.94	0.015	**17.77**	**<0.001**
3	Association was not found	1–12	2.48	0.116	0.04	0.845	0.41	0.552
4	12 reference genes	20–517	***42.39***	***<0.001***	***9.26***	***0.002***	0.05	0.823
5	**12 circadian clock genes**	50–537	***16.07***	***<0.001***	0.12	0.729	5.64	0.018
6	**12 skin pigmentation genes**	95–446	3.01	0.083	7.77	0.005	**29.16**	**<0.001**
7	**Among reference genes**	8–7	2.56	0.109	**25.05**	**<0.001**	**55.87**	**<0.001**
8	**Among circadian clock genes**	20–5	**14.75**	**<0.001**	**78.75**	**<0.001**	**141.30**	**<0.001**
9	**Among skin pigmentation genes**	63–9	**36.35**	**<0.001**	**155.78**	**<0.001**	**234.84**	**<0.001**
10	Associates of type 2 diabetes	2–32	6.48	0.011	–	–	0.25	0.616
11	Associates of BMI	2–32	6.48	0.011	–	–	0.25	0.616
12	Associates of sleep traits	3–31	4.66	0.031	–	–	1.58	0.209
13	Associates of bipolar disorder	3–31	4.66	0.031	–	–	1.58	0.209
14	Associates of schizophrenia	5–29	2.14	0.144	–	–	6.03	0.008
15	Associates of sclerosis	4–30	3.24	0.072	–	–	3.86	0.049
16	**Associates of chronotype**	10–24	–	–	**11.00**	**<0.001**	**30.43**	**<0.001**
17	**Associates of skin pigmentation**	10–24	0	1.000	**11.00**	**<0.001**	**30.43**	**<0.001**
18	Associates of two traits/diseases	7–27	0.71	0.401	3.81	0.051	**14.94**	**<0.001**
19	**SNPs under positive selection**	8–26	0.30	0.583	5.86	0.016	**19.70**	**<0.001**
20	*HMGA1P7*	0–34	***11.72***	***0.001***	3.44	0.064	–	–
21	*NBPF13P*	0–34	***11.72***	***0.001***	3.44	0.064	–	–
22	*NBPF22P*	0–34	***11.72***	***0.001***	3.44	0.064	–	–
23	*TBC1D3P1-DHX40P1*	1–33	8.79	0.003	1.54	0.215	–	–
24	*COL6A4P2*	2–32	6.48	0.011	0.43	0.513	–	–
25	*DTX2P1-UPK3BP1-PMS2P11*	1–33	8.79	0.003	1.54	0.215	–	–
26	*ANKRD62P1-PARP4P3*	5–29	2.14	0.144	0.94	0.334	–	–
27	*PTENP1*	2–32	6.48	0.011	0.43	0.513	–	–

Notes: List of polymorphisms in **bold**: Significantly **higher** fraction was expected for this set of polymorphisms. Significance of differences in fraction was tested in comparison with the sets of polymorphisms revealed by a GWAS of chronotype (# 16) or skin pigmentation (# 17), 6 other GWAS studies (## 10–15), and in 8 pseudogenes (## 20–17). Results of χ^2-test in **bold** or ***bold italic***: Pairwise comparison revealed significantly **higher** or significantly ***lower*** fraction of polymorphisms meeting the triple criterion (after correction for 25 or 21 or 19 tests, $p < 0.0020$ or 0.0024 or 0.0026, respectively). #: Number of a set of polymorphisms in order; *: Illustrated in Figure 1.

representing 8 pseudogenes (## 20–27), 8 associates of traits/diseases from GWASs (## 10–18) and two meta-analyses of GWASs (## 18, 19).

Three sets of 537, 587, and 541 polymorphisms (## 4–6) represent, respectively, 12 reference genes (*DBH*, *SLC6A3*, *DRD3*, *NPSR1*, *BDNF*, *CACNA1C*, *ACE*, *ACTN3*, *PPARA*, *GRIK3*, *TMEM132D*, and *BRAF*), 12 circadian genes (*PER1*, *PER2*, *PER3*, *CLOCK*, *TIM*, *RORC*, *RORA*, *ARNTL*, *NPAS2*, *NFIL3*, *NR1D1*, and *CSNK1E*) and 12 skin pigmentation genes (*TMEM138*, *DDB1*, *TYRP1*, *MC1R*, *SLC24A5*, *SLC45A2*, *MFSD12*, *KITLG*, *TYR*, *OCA2*, *GRM5*, and *HERC2*). The maximal number of polymorphisms per gene was limited to 80. Like the selection of polymorphisms from pseudogenes, the selection of loci from any of these genes started from the last of the listed polymorphisms and was completed at the 2nd-80th polymorphism with GMAF > 0.2. The genes responsible for the differences in skin color were previously identified in several studies (Sturm 2009; Beleza et al. 2013; Jablonski and Chaplin 2013; Crawford et al. 2017). Some of the polymorphisms in reference genes were previously associated with individual differences in dopaminergic neurotransmission (*DBH*, *SLC6A3* and *DRD3*; Paclt et al. 2004; Corominas et al. 2009; Mandelli and Serretti 2013; Gray and MacKillop 2014), mental disorders (*NPSR1*, *BDNF* and *CACNA1C*; Muglia et al. 2003; Schumacher et al. 2005; Bhat et al. 2012; Howe et al. 2016), achievements in sport (*ACE*, *ACTN3* and *PPARA*; reviewed by Ahmetov and Fedotovskaya (2015), Ahmetov et al. (2016) and neurobehavioral functioning (*GRIK3*, *TMEM132D* and *BRAF*; Minelli et al. 2009; Erhardt et al. 2012; Hodgson et al. 2016; Theofanopoulou et al. 2017).

From each of these three groups of genes, a set of strong correlates of latitude was additionally identified (Putilov et al. 2018) and they were included in three separate sets to represent most probable targets of latitude-dependent selection (## 7–9). As it was mentioned in Introduction, we also previously published some results on correlation between latitude and polymorphisms tested in the candidate gene studies of chronotype (## 1–3). One set includes 7 tested SNPs from 5 circadian clock genes (Dorokhov et al. 2018) and each of 2 other sets include 13 SNPs in 10 circadian clock genes that either showed or did not show significant association with chronotype in the previous candidate gene studies (Putilov et al. 2018).

If alleles under selection increase in prevalence in a population, they are expected to leave distinctive genetics-based signatures (patterns of genetic variation) in DNA sequence. However, a great challenge for a search for such signatures is determining whether a given pattern is due to selection or to the confounding effects of population demographic history that include bottlenecks (periods of reduced population size) and expansions (Kelley et al. 2006; Sabeti et al. 2006). Both the genetic bottleneck and the following rather rapid increase of effective population size had occurred after the out of Africa migration and dispersal of the ancestors of Eurasians (Lippold et al. 2014). Hence, 16 Eurasian populations share common demographic history that was different from this history for 5 African populations. In order to more reliably identify which of genetic variants harbors a latitude-dependent adaptation we previously suggested and applied an approach relying on combination of three single criteria of such adaptation (Putilov et al. 2018) These are the criteria of an enlarged level of population differentiation in Eurasia compared to Africa (11 Eurasian vs. 5 African samples), a correlation between latitude and genetic variation in Eurasia (only 11 Eurasian samples), and a correlation between latitude and genetic variation in both Eurasia and Africa (all 16 samples). The complementary results for three single criteria allow separation of the effects of selection from most of confounding effects of population demographic history (Putilov et al. 2018).

More specifically, an allele was defined as major allele when its frequency was found to be higher than 0.500 after averaging frequencies calculated for 5 African samples. Frequency of this allele (MaAF) was subjected to further analysis of its geographic variation. Given that African populations always evolved in near equatorial regions in contrast to Eurasian populations that were exposed at higher latitudes to such novel environmental factor as seasonal variations in day length, we tested the expectation that standard deviation (SD) of MaAF calculated for Eurasian samples is significantly larger than that obtained for African samples. SDs of MaAFs for 11 Eurasian and 5 African samples were compared with Levene's test for equality of variances ($p < 0.05$ for SD). Spearman rank coefficient of correlation (ρ) was applied to measure spatial relationship between MaAF and the distance of the recent place of populations' residence from the equator (latitude, degree North). Either 16 (African + Eurasian) or 11 samples (only Eurasian) were included in such correlation analysis (either ρ_{16} or ρ_{11}, respectively, $p < 0.05$ for both). A resemblance between correlation patterns was interpreted as a sign of adaptive rather than demographic genetic history. A stronger multiple (dual or triple) criterion was provided by combination of these single criteria (SD, ρ_{16} and ρ_{11}, $p < 0.05$ for each). Table 1 reports the results obtained for each of such 4 possible multiple criteria applied to each of 27 sets of polymorphisms.

The SPSS statistical software package (IBM, Armonk, NY, USA, version 22.0) was used to perform χ^2-test for checking statistical significance of differences in fraction of these polymorphisms between the 27 sets (Figure 1 and Tables 1 and 2) as well as between the groups of these sets (Table 3).

Moreover, principal component analysis was performed for reducing each set of MaAFs to a more manageable single score on the 1st (largest) principal component. It is expected that this score can be found to be a significant correlate of latitude when a rather big fraction of MaAFs of a given set of polymorphisms varies with latitude (Dorokhov et al. 2018). We also expected that the correlation between latitude and the 1st principal component score (Table 4) can be further strengthened by combining several sets in a larger group of polymorphisms representing the same or similar latitude-dependent adaptations (Table 5). The two applied approaches to calculation of the 1st principal component score for such groups are explained in more details in the legends to Figures 2 and 3 and notes to Tables 5 and 6.

Results

In Tables 1–6, the sets of polymorphisms and groups of sets of polymorphisms for which the latitude-dependent selection was expected are printed in bold. These are (1) loci showing association with chronotype in the previously published candidate genes studies (## 1 and 2 in Table 2), (2) polymorphic variants in circadian clock genes and skin pigmentation genes (## 5 and 6, (3) loci showing strong correlation with latitude (## 7–9), (4) polymorphisms hinted by GWASs of chronotype and skin pigmentation (## 16 and 17), and (5) showing the signs of recent positive selection (# 19). Table 1 illustrates that dual criteria for such selection were met by a large proportion of polymorphisms from these highlighted sets. However, these dual criteria were also met by many loci from other sets (Table 1). The differentiations between the sets of polymorphisms became much clearer when the strongest triple criterion was applied (Tables 1–3). In particular, more than 20% of polymorphisms from the sets of 34 associates of chronotype and skin pigmentation met this triple criterion, whereas it was met by less than 15% of polymorphisms in reference genes and pseudogenes (Table 1).

Table 3. Pairwise comparison of groups of polymorphisms meeting the triple criterion.

Triple criterion ($p < 0.05$: SD, ρ_{16} and ρ_{11})		Met		**Vs. # 16**		Vs. ## 10–15		Vs. ## 20–27	
#	Group of sets of polymorphisms	Yes	No	χ^2	p	χ^2	p	χ^2	p
2–3	Association was/was not found	5	21	0.81	0.370	2.43	0.119	**10.77**	**0.001**
4–6	All 36 genes	165	1500	***13.72***	***<0.001***	0.07	0.787	**9.74**	**0.002**
5–6	**24 pigmentation and clock genes**	145	983	***7.83***	***0.005***	2.01	0.157	**17.18**	**<0.001**
7–9	**Strong correlates of latitude**	91	21	**32.87**	**<0.001**	**164.88**	**<0.001**	**242.42**	**<0.001**
10–15	Reference associates from GWAS	19	185	***11.00***	***0.001***	–	–	5.48	0.019
16–19	**Other GWAS and meta-analyses**	35	101	–	–	**16.47**	**<0.001**	**42.65**	**<0.001**
20–27	8 pseudogenes	11	261	***30.43***	***<0.001***	5.48	0.019	–	–

List of polymorphisms in **bold**: Significantly **higher** fraction was expected for a group including two or more sets of polymorphisms. Results of χ^2-test in **bold** or ***bold italic***: Pairwise comparison suggested significantly **higher** or significantly ***lower*** fraction of polymorphisms meeting the triple criterion (after correction for 6 tests, $p < 0.0083$, respectively). #: Sets of polymorphisms numbered in order (Table 2).

Similar results were shown by the correlates of chronotype identified in the candidate gene studies of our and other groups (Table 1). Notably, this triple criterion was met only by a half of those 15 polymorphisms from 537 variants located in the reference genes that was found to show a highly significant correlation with latitude ($-0.8366 < \rho_{16} > 0.8366$). In contrast, much higher fraction (>80%) was revealed among 25 and 72 similar polymorphisms from 587 to 541 variants located in the circadian and pigmentation genes, respectively (Table 1). As illustrated in Figure 1, all differences between 27 sets of polymorphisms in this fraction were found to be in expected direction.

As indicated by χ^2-test (Tables 2 and 3), the fraction of 10 polymorphisms that met the triple criterion among 34 associates of chronotype (# 16) or skin pigmentation (# 17) was significantly higher than the fractions of polymorphisms sampled from pseudogenes (## 20–22) and from protein-coding regions of reference genes (# 7) and circadian clocks genes (# 8). This fraction was also significantly higher than the fraction in the group of associates of 6 other traits/diseases hinted by GWASs (## 10–15). The difference did not reach a statistically significant level (Tables 2 and 3) in the comparison with two sets of polymorphisms from the meta-analysis of GWASs that identified the associates of two traits/diseases (# 17) and SNPs with the signs of positive selection (# 18).

Very similar results were yielded by a search for significant correlation between latitude and score on the 1st principal component (Table 4). The only exception was an unexpectedly strong correlation coefficient obtained for one of 8 pseudogenes. However, this correlation was positive unlike any other correlations reflecting a general tendency for reduction of MaAF with increase of latitude (Table 4).

Further grouping of polymorphisms from several sets of loci to represent the same and similar latitude-dependent adaptations led to strengthening correlation between latitude

Table 4. Correlation of latitude with 27 scores on the 1st principal component.

#	Samples from continent/s Correlation and its significance	VE%	Africa + Eurasia ρ_{16}	 p	Only Eurasia ρ_{11}	 p	Reference (source of lists of marker names)
	Polymorphisms in circadian clock genes tested as markers of chronotype or sleep times						
1	**Association was found (partly)**	53	**−0.941**	**<0.001**	**−0.893**	**<0.001**	Dorokhov et al. (2018)
2	**Association was found**	59	**−0.898**	**<0.001**	**−0.834**	**0.001**	Putilov et al. (2018)
3	Association was not found	39	−0.414	0.111	0.610	0.046	
	1665 polymorphisms with MAF > 0.200 selected from 36 genes of three groups						
4	12 reference genes	56	−0.380	0.147	0.715	0.013	Putilov et al. (2018)
5	**12 circadian clock genes**	45	−0.395	0.130	0.711	0.014	
6	**12 skin pigmentation genes**	62	**−0.838**	**<0.001**	−0.565	0.070	
	112 strong correlates of latitude ($-0.8366 < \rho_{16} > -0.8366$) among 1665 polymorphisms						
7	**Among reference genes**	86	**−0.938**	**<0.001**	**−0.856**	**0.001**	
8	**Among circadian clock genes**	89	**−0.925**	**<0.001**	**−0.843**	**0.001**	
9	**Among skin pigmentation genes**	90	**−0.906**	**<0.001**	−0.747	0.008	
	204 reference polymorphisms listed in 6 GWAS studies of associates of traits/diseases						
10	Associates of type 2 diabetes	54	−0.442	0.087	0.519	0.102	Morris et al. (2012)
11	Associates of BMI	40	−0.607	0.013	−0.041	0.905	Locke et al. (2015)
12	Associates of sleep traits	46	−0.426	0.100	0.656	0.028	Goel (2017)
13	Associates of bipolar disorder	47	0.318	0.230	−0.729	0.011	Ikeda et al. (2017)
14	Associates of schizophrenia	51	−0.633	0.008	−0.087	0.800	Schizophrenia (2014)
15	Associates of sclerosis	46	−0.679	0.004	−0.210	0.536	Schymick et al. (2007)
	68 polymorphisms listed in two GWAS studies of associates of latitude-related traits						
16	**Associates of chronotype**	44	**−0.875**	**<0.001**	−0.811	0.002	Kalmbach et al. (2017)
17	**Associates of skin pigmentation**	63	**−0.839**	**<0.001**	−0.610	0.046	Stokowski et al. (2007)
	68 polymorphisms from two meta-analyses of associates of traits/diseases						
18	Associates of two traits/diseases	45	**−0.884**	**<0.001**	−0.815	0.002	Hindorff et al. (2009)
19	**SNPs under positive selection**	49	**−0.909**	**<0.001**	−0.797	0.003	
	272 polymorphisms from 8 pseudogenes						
20	*HMGA1P7*	74	0.554	0.026	−0.232	0.492	Present analysis
21	*COL6A4P2*	65	−0.381	0.145	0.656	0.028	
22	*NBPF13P*	62	−0.642	0.007	−0.551	0.079	
23	*NBPF22P*	50	**0.758**	**0.001**	0.506	0.113	
24	*TBC1D3P1-DHX40P1*	91	0.591	0.016	−0.009	0.979	
25	*DTX2P1-UPK3BP1-PMS2P11*	74	−0.315	0.204	0.820	0.002	
26	*ANKRD62P1-PARP4P3*	58	−0.672	0.004	−0.178	0.601	
27	*PTENP1*	66	0.411	0.114	−0.583	0.060	

Notes: MaAFs of each of 27 sets of polymorphisms were subjected to principal component analysis and scores on the 1st principal component were correlated with latitude using data from either 16 or 11 populations (Africa + Eurasia or Only Eurasia, respectively). Spearman coefficient of correlation was expected to be **significant** for the set of polymorphisms printed in **bold**. Correlation is printed in **bold** when it remained **significant** after correction for 27 tests ($p = 0.0019$). VE%: Percentage of total variance explained by the 1st principal component.

Table 5. Correlation of latitude with second-order and total scores on the 1st principal component.

Samples from continent/s		VE%	Africa + Eurasia		Only Eurasia	
Correlation and its significance	*n*		ρ_{16}	*p*	ρ_{11}	*p*
Second-order score on the 1st principal component						
Circadian clocks-related traits*	5	86	**−0.934**	**<0.001**	**−0.884**	**<0.001**
Other (non-circadian) selected traits**	5	91	**−0.941**	**<0.001**	**−0.838**	**0.001**
Reference associates of traits/diseases (GWAS)	6	91	−0.411	0.114	0.610	0.046
Pseudogenes	8	71	−0.536	0.032	0.246	0.466
Score on the 1st principal component of variation in MaAFs of a group						
Circadian clocks-related traits***	64	78	**−0.929**	**<0.001**	**−0.879**	**<0.001**
Other (non-circadian) selected traits	131	85	**−0.909**	**<0.001**	**−0.784**	**0.004**
Reference associates of traits/ diseases (GWAS)	19	84	**−0.866**	**<0.001**	−0.679	0.022
Pseudogenes	11	87	**−0.878**	**<0.001**	**−0.843**	**0.001**

Notes: Upper part. Scores on the 1st principal component for 5–8 sets were grouped for representing polymorphisms related to chronotype and other circadian clocks' traits (## 1, 2, 5, 8 and 16 in Table 1), other (non-circadian) selected traits (## 6, 7, 9, 17 and 19), other traits/diseases from 6 GWAS studies (## 10–15) and 8 pseudogenes (## 20–27). The scores of a group were subjected to principal component analysis for calculating second-order scores on the 1st principal component. Lower part. The polymorphisms meeting triple criterion (Table 3) were included into the same 4 groups consisting of 11–131 polymorphisms and their MaAFs were subjected to principal component analysis to obtain 4 total scores on the 1st principal component. The calculated 4 second-order scores and 4 total scores (upper and lower parts of the table, respectively) were correlated with latitude using datasets from either 16 or 11 populations (Africa + Eurasia or only Eurasia, respectively). Groups of polymorphisms printed in **bold**: Significant correlation was expected for these scores on the 1st principal component. Correlation in **bold**: Correlation remained significant after correction for 8 tests ($p < 0.006$). VE%: Percentage of total variance explained by the 1st principal component; n: Number of analyzed scores on the 1st principal component or number of analyzed MaAFs (upper and lower parts of the table, respectively); *: Illustrated in Figure 2(A); **: Illustrated in Figure 2(B); ***: Illustrated in Figure 3(A).

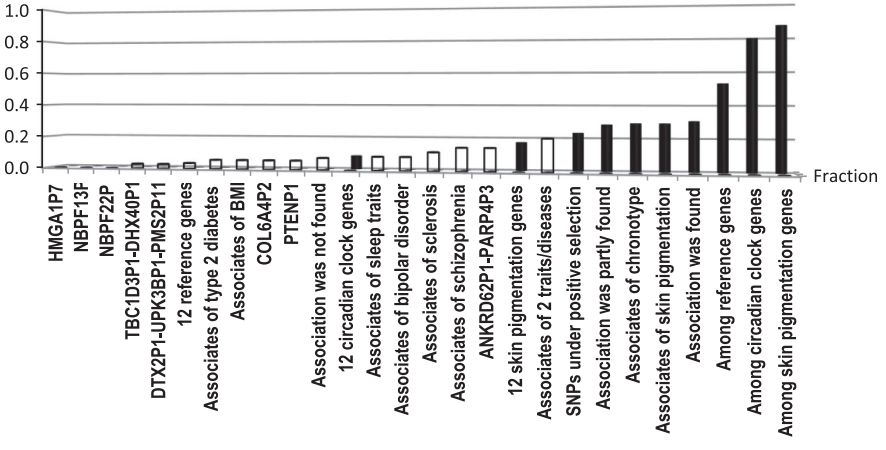

Figure 1. Fraction of polymorphisms meeting the triple criterion of latitude-related selection.

Notes: Fraction: Fraction of polymorphisms meeting the triple criterion ($p < 0.05$ for SD, ρ_{16}, and ρ_{11}) in 27 sets of polymorphisms shown in Table 2.The sets were ordered from the lowest to highest fraction. The single criterion of SD is an increased standard deviation (SD) of MaAF (Major Allele Frequency) in 11 Eurasian samples as compared to 5 African samples (Levene's test for equality of variances, $F > 4.59$, df = 14, $p < 0.05$); the single criterion of ρ_{16} is a correlation between latitude and MaAF obtained for 16 (African and Eurasian) samples (−0.5< Spearman coefficient of correlation >0.5, $n = 16$, $p < 0.05$), and the single criterion of ρ_{11} is a correlation between latitude and MaAF obtained for 11 (only Eurasian) samples (−0.6< Spearman coefficient of correlation >0.6, $n = 11$, $p < 0.05$). Significantly higher fraction was expected for the sets of polymorphisms shown as black columns compared to the corresponding sets shown as white columns. See also the list of these 27 sets and their fractions in Tables 1 and 2.

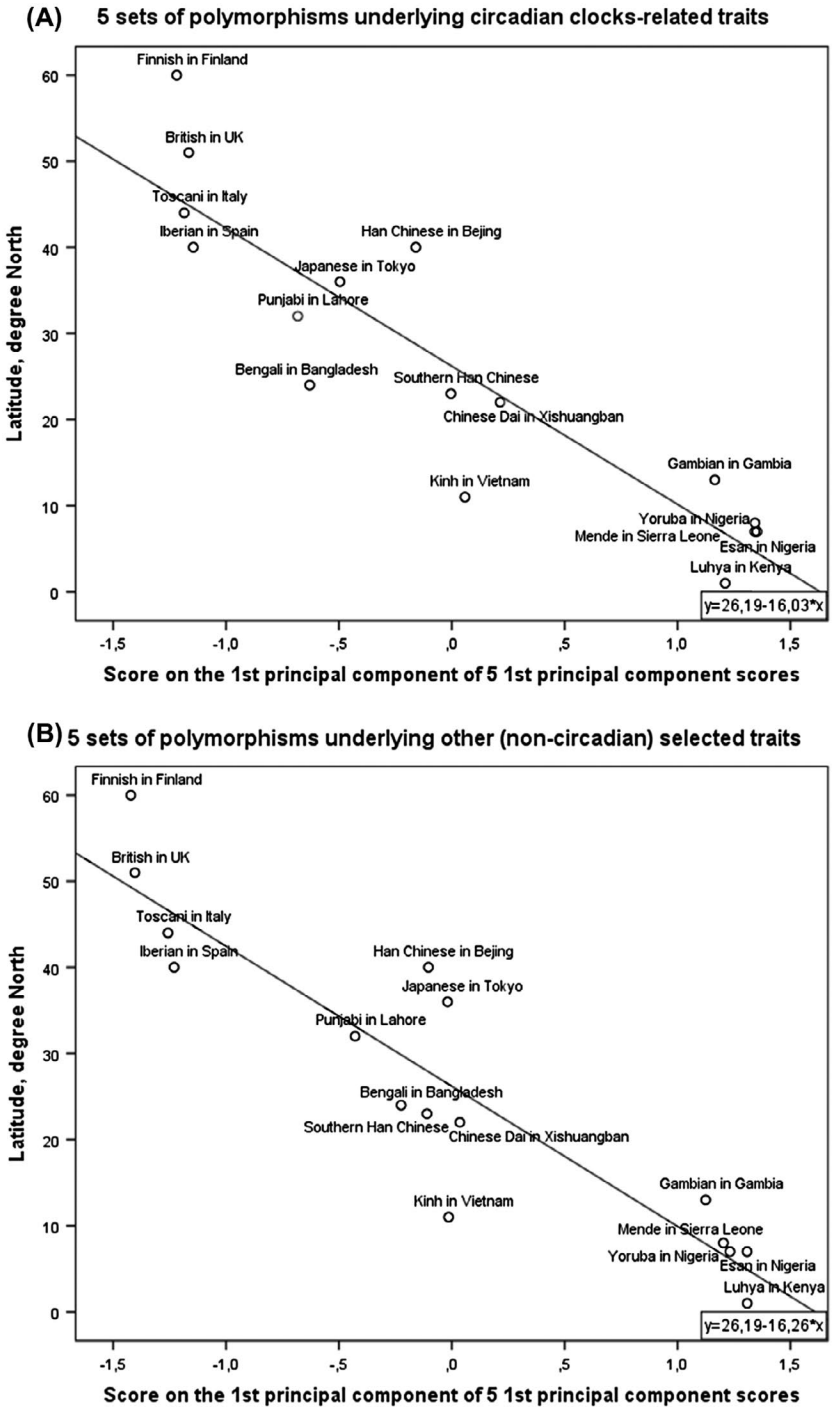

Figure 2. Latitude by second-order score on the 1st principal component.

Notes: Principal component analysis was applied to MaAFs of sets of polymorphisms representing variation in circadian clocks-related traits (## 1, 2, 3, 8 and 1 in Table 1) and other (non-circadian) selected traits (## 6, 7, 9, 17 and 19). The obtained sets of 5 scores on the 1st principal component were subjected to principal component analysis that yielded second-order scores on the 1st principal component. Lines illustrate linear trends for relationship between latitude and such second-order scores on the 1st principal component for polymorphisms underlying circadian clocks-related traits (A) and other (non-circadian) selected traits (B). See also Spearman coefficients of correlation reported in Table 5.

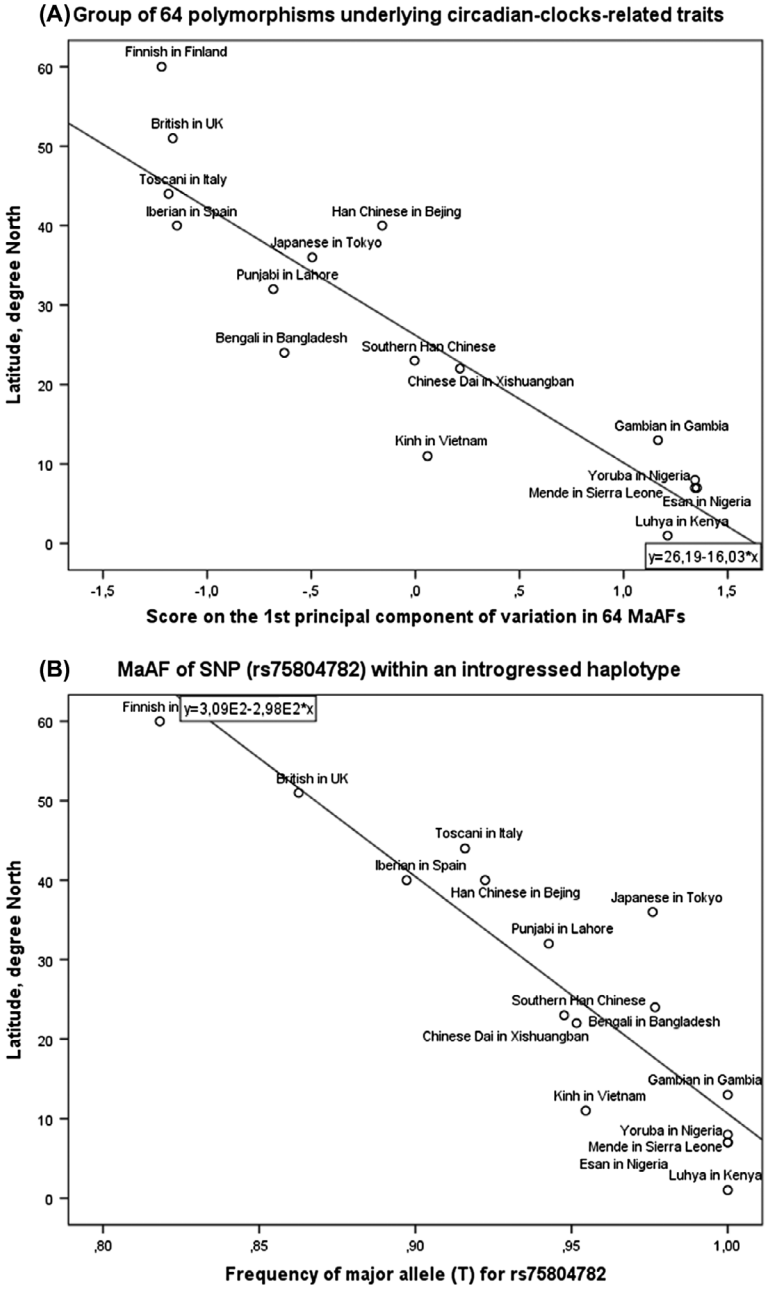

Figure 3. Latitude by total score on the 1st principal component and by MaAF of rs75804782.

Notes: A. The group of analyzed polymorphisms includes 64 polymorphisms meeting triple criterion from circadian clocks genes (54) and associates of chronotype (10). Their MaAFs were subjected to principal component analysis to obtain the total score on the 1st principal component of variation in 64 MaAFs. This score was plotted against latitude. See also the Spearman coefficient of correlation with latitude reported in Table 5, the Spearman coefficient of correlation between this total score and the corresponding second-order score reported in Table 6, and compare with the pattern of correlation for this corresponding score illustrated in Figure 2(A). B. An archaic allele C of rs75804782 near *ASB1* was mapped within an introgressed haplotype. Its correlation with latitude was the strongest among the correlations of allele frequencies calculated for those 10 SNPs-associates of chronotype that met the triple criterion. Spearman coefficients of correlation between latitude and African variant (T) attained the values of −0.916 and −0.831 for 16 (African + Eurasian) and 11 (only Eurasian) samples ($p < 0.001$ and $p = 0.002$, respectively).

Table 6. Correlation between second-order and total scores on the 1st principal component.

4 total scores ↓ and 2 second-order scores →		Second-order score on the 1st principal component			
Score on the 1st principal component of variation in MaAFs of a group	*n*	**Circadian clocks-related traits**		**Other (non-circadian) selected traits**	
Circadian clocks-related traits	26	**$\rho = 0.981$**	**$p < 0.001$**	$\rho = 0.899$	$p < 0.001$
Other (non-circadian) selected traits	26	$\rho = 0.894$	$p < 0.001$	**$\rho = 0.986$**	**$p < 0.001$**
Reference associates of traits/diseases (GWAS)	26	$\rho = 0.882$	$p < 0.001$	$\rho = 0.962$	$p < 0.001$
Pseudogenes	26	$\rho = 0.863$	$p < 0.001$	$\rho = 0.950$	$p < 0.001$

Notes: Using data on 26 samples of the 1000 genomes project, Spearman coefficients of correlation were calculated between second-order and total scores on the 1st principal component (see Table 5). Groups of polymorphisms printed in **bold**: for the same group of polymorphisms, scores on the 1st principal component were expected to be practically identical. Correlation in **bold**: Correlation coefficient attained a value higher than **0.980**; *n*: Number of populations of the 1000 Genomes Project Phase 3.

and the 1st principal component score (Table 5). These correlations (Figures 2 and 3(A)) were found to be stronger than the vast majority of correlations of MaAFs of single polymorphisms including any of 34 polymorphisms-associates of chronotype. Among them the strongest correlate of latitude was a variant rs75804782 near ASB1 (minor allele C) located within one of introgressions of the Neanderthal's genome into the genomes of Eurasians (Figure 3(B)).

Practically identical results were yielded by inter-correlating the 1st principal component scores obtained using two different methodologies (Table 6; see the legend to Figures 2 and 3 for more details). Consequently, the patterns of correlation with latitude demonstrated by these scores (second-order score and total score) were also practically identical (compare Figure 2(A) and Figure 3(A)).

Discussion

The racial and latitude-dependent differences in chronotype were reported in the chronobiological literature and it is reasonable to expect that they can be, at least, partly explained by polygenic latitude-dependent selection of polymorphic variants underlying individual variation in chronotype. The GWAS findings allowed the paradoxical prediction of higher rate of polymorphisms with the genetic signatures of latitude-dependent selection among the associates of chronotype than among protein-coding regions of the circadian clock genes. Results of the present analysis consistently supported this and several other predictions concerning probability to identify polymorphisms with genetic signatures of latitude-dependent selection. We found that these signatures were more frequently yielded among associates of chronotype than among polymorphisms sampled from pseudogenes, protein-coding regions in either circadian clock genes or reference genes and in the sets of polymorphisms hinted by GWASs of other traits/diseases. The expected exceptions were those sets of polymorphisms that, like chronotype, can be shaped by latitude-dependent adaptations.

Interestingly, we noted that among 34 associates of chronotype, the strongest correlation with latitude was shown by a SNP introgressed in the genomes of Eurasians from the Neanderthal's genome. As can be seen in Figure 3(B), only T allele was found in African

populations and an increase in frequency of the Neanderthal's C allele with latitude was the major cause of the emergence of highly significant correlation. These results on geographic variation in allele frequency of rs75804782 are complementary to the results previously reported in publication of Dannemann and Kelso (2017) who used frequencies of rs75804782 alleles provided by another data-set (the Simons Genome Diversity Panel).

The comparison of the set of 34 loci-associates of chronotype/skin pigmentation with some of 6 34-polymorphism sets of polymorphisms-associates of other traits/diseases did not reveal statistically significant differences (Table 2). It seems that the small size of these samples cannot be the only reason for such negative finding. Another plausible explanation would be that these traits/diseases were also shaped by latitude-dependent selection to more or less extent. Such possibility might be exemplified by findings on schizophrenia. The tendencies for schizophrenia prevalence to increase with latitude were found to be large, significant and present on several continents, hypothetically, due to a role playing by prenatal vitamin D deficiency in this condition (Kinney et al. 2009). In fact, it is an uneasy task to name a trait/disorder for which a correlation with a latitude-related environmental factor can be fully excluded. For instance, prevalence of type 2 diabetes was found to be positively associated with ambient temperature (Speakman and Heidari-Bakavoli 2016), and a similar association can be predicted for BMI because human populations, like populations of many other mammals, are following the Bergmann's and Allen's Rules (e.g. Foster and Collard 2013).

Because it is likely that latitudinal and racial differences in chronotype were, at least partly, shaped by polygenic latitude-dependent adaptation to seasonal variation in day length at higher latitudes, we recommended to prioritize genes-markers of chronotype by selecting most promising loci with MaAF showing a strong correlation with latitude and a heightened level of population differentiation in Eurasia (Dorokhov et al. 2018; Putilov et al. 2018). However, future candidate gene studies are still required to examine prospects of such approach aimed on a search for associates of this trait among loci harboring latitude-dependent adaptations.

In sum, latitudinal and racial differences in chronotype can be, at least partly, caused by polygenic latitude-dependent adaptation to seasonal variation in day length at higher latitudes. The findings of genome-wide association studies (GWASs), such as the mapping 34 polymorphisms-associates of chronotype in non-protein-coding DNA sequences, allow a paradoxical prediction of higher probability to identify genetic signatures of latitude-dependent adaptation among these 34 variants than among variants in protein-coding DNA regions including the circadian clock genes. Comparison of geographic variation in allele frequencies in this set of 34 polymorphisms with variation in 26 other sets supported several predictions concerning direction and significance of differences between these sets in fraction of polymorphisms with the signatures of latitude-dependent adaptation. We found that such signatures as a correlation of allele frequency with latitude and a larger level of population differentiation in Eurasia than in Africa were more common in the set of 34 associates of chronotype than in the sets of loci hinted by GWASs of several other traits/diseases, sampled from pseudogenes and from protein-coding regions of either circadian clock genes or reference genes. Moreover, the results supported the prediction of non-significance of difference from the sets of loci representing other traits shaped by latitude-dependent adaptations, such as skin pigmentation. It was also noted that the strongest correlate of latitude among 34 chronotype-associated polymorphisms was a variant introgressed in the genomes of Eurasians from the Neanderthal's genome (allele C of rs75804782 near ASB1). It seems

that aiming future candidate gene studies on examination of association between chronotype and loci harboring latitude-dependent adaptations would be a promising approach to prioritization of polymorphisms-markers of this trait.

Disclosure statement

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