University of Groningen

CLOCK Gene Variants Associate with Sleep Duration in Two Independent Populations

Allebrandt, Karla V.; Teder-Laving, Maris; Akyol, Mahmut; Pichler, Irene; Mueller-Myhsok, Bertram; Pramstaller, Peter; Merrow, Martha; Meitinger, Thomas; Metspalu, Andreas; Roenneberg, Till

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Link to publication in University of Groningen/UMCG research database

Supplemental Information

Supplemental Results

Average sleep duration for subjects having different genotypes and haplotypes for rs12649507 and rs11932595.

In the discovery sample, subjects carrying AA for the SNP rs12649507 slept on average 34 minutes less than those carrying GG. In the confirmation sample, this value was 22 minutes (Figure 4A). Subjects carrying GA at the same locus slept 12 minutes less (12.5 minutes in the confirmation sample) than those carrying GG, and 22 minutes more (9 minutes in the confirmation sample) than those carrying AA (Figure 4A). Subjects carrying AA for the SNP rs11932595 slept on average 28 minutes less (21 minutes more in the confirmation sample) than GG homozygotes (Figure 4A). The heterozygous GA population slept 26 minutes less (3 minutes more in the confirmation sample) than GG homozygous, and 2 minutes more (23 minutes less in the confirmation sample) than AA homozygous (Figure 4A).

The shortest average sleep duration associated with rs12649507/rs11932595 occurred for subjects carrying AAGA in the discovery sample, and for those subjects carrying AAGG in the confirmation sample. The longest sleep duration was associated with GGGG in the discovery sample, but in the confirmation sample, GGAA was most often associated with long sleep, followed by AAAA (Figure 4B).

Table S1. Fits for normalized sleep duration. The large amount of data available per age group in the Central European databank allowed the calculation of fits independently for the age groups of young (ages 10 to 20) and adult (ages 21 to 71) subjects (Figure 1A). Only one fit was calculated for the Estonian sample (ages 18 to 65), as due to lack of younger subjects, a separate fit for teen-agers was not possible (Figure 1B). Sleep duration for South Tyrolean subjects were normalized based on the large Central European database because the small number of Tyrolean subjects did not allow a separate age correlation (Figure 1).

Age groups	Females	Males
	Central European databank	
10 to 20	$y = 0.0259x^2 - 0.9299x + 16.176$	$y = 0.0146x^2 - 0.6001x + 13.711$
21 to 71	$y = 5.543793E\text{-}04x^2 - 6.106019E\text{-}02x + 8.978627E+00$	$y = 0.0008x^2 - 0.0747x + 8.8976$
	Estonian sample	
18 to 65	$y = 0.0005x^2 - 0.0585x + 9.3738$	$y = 0.0006x^2 - 0.059x + 9.1278$

Table S2. List of SNPs genotyped in the discovery sample. SNP_ID indicates the SNP rs identification code, and the HWE_p column presents the Hardy-Weinberg equilibrium P values. Dashed lines mean that genotyping call rate was under threshold and the respective variables could not be estimated.

SNP_ID	Genome-wide location	Gene1	Function	Mutation	Alleles	HWE_p	Mono-morphic	Minor allele frequency
rs707455	1007759577	VAMP3	Prom	-	C/T	0.4520	No	0.3871
rs707458	1007766478	VAMP3	In	-	A/G	----.	----	----
rs12078704	1007779222	VAMP3	3'UTR	-	C/T	.	Yes	0.0000
rs11121023	1007782823	VAMP3	3'UTR	-	A/G	0.7608	No	0.2419
rs228644	1007800349	PER3	In	-	A/G	----	----	----
rs10746473	1007812322	PER3	In	-	A/G	0.0408	No	0.3511
rs10462018	1007813893	PER3	In	-	C/T	0.1181	No	0.1444
rs697690	1007818846	PER3	In	-	C/T	0.0389	No	0.3059
rs228697	1007821845	PER3	Ex	P856A	C/G	0.1357	No	0.1238
rs2640908	1007824207	PER3	Ex	T969T	C/T	0.0135	No	0.1429
rs12750400	1007824335	PER3	Ex	S1012L	C/T	.	Yes	0.0000
rs2640909	1007824383	PER3	Ex	M1028T	C/T	0.7625	No	0.3100
rs228665	1007825222	PER3	In	-	C/G	0.5795	No	0.3628
rs2640905	1007830142	PER3	Ex	S1081C	C/G	.	Yes	0.0000
rs10462021	1007831399	PER3	Ex	H1149R	A/G	.	Yes	0.0000
rs1150394	1007834661	UTS2	3'UTR	-	A/T	0.7792	No	0.4156
rs3849381	2100910337	NPAS2	In	-	A/G	0.2635	No	0.3137
rs1561002	2100923789	NPAS2	In	-	C/T	----	----	----
rs965519	2100928867	NPAS2	In	-	A/G	0.4457	No	0.1734
rs7598826	2100931952	NPAS2	In	-	A/G	0.8624	No	0.4736
rs2871389	2100953692	NPAS2	In	-	C/T	0.2060	No	0.3318
rs6721366	2100966981	NPAS2	In	-	C/G	0.0686	No	0.2138
rs12712083	2100967417	NPAS2	In	-	A/G	0.7801	No	0.4720
rs12712084	2100967507	NPAS2	In	-	C/T	0.9500	No	0.4705
rs1369481	2100970477	NPAS2	In	-	A/G	0.1995	No	0.2988
rs2117713	2100980485	NPAS2	In	-	C/T	0.4447	No	0.1682
rs4851377	2100980784	NPAS2	In	-	C/T	0.9644	No	0.4876
rs13394520	2100982328	NPAS2	In	-	A/G	0.0341	No	0.3742
rs356655	2100987933	NPAS2	In	-	A/G	0.9428	No	0.3438
rs11894370	2100991428	NPAS2	In	-	A/G	----	----	----
rs356643	2100994710	NPAS2	In	-	A/G	0.3415	No	0.4969
rs6725296	2100996222	NPAS2	In	-	A/G	0.0657	No	0.2121
rs17717414	2101005068	NPAS2	In	-	A/G	0.0763	No	0.1724
rs3754674	2101008279	NPAS2	In	-	C/G	0.8279	No	0.4087
rs13025524	2101008699	NPAS2	In	-	A/G	0.3299	No	0.3742
rs4851381	2101009313	NPAS2	In	-	G/T	----	----	----
rs3768984	2101009505	NPAS2	In	-	A/C	0.6253	No	0.2309
rs4851383	2101019276	NPAS2	In	-	A/G	0.0000	No	----
rs10206435	2101021020	NPAS2	In	-	C/G	0.2789	No	0.4829
rs12712085	2101023669	NPAS2	In	-	A/G	0.3069	No	0.4003
rs3820787	2101024752	NPAS2	In	-	A/G	0.5490	No	0.3634
rs11673746	2101027661	NPAS2	In	-	C/T	0.2270	No	0.3966
rs4851390	2101030223	NPAS2	In	-	A/G	0.5997	No	0.1590
rs895520	2101036455	NPAS2	In	-	C/T	0.1884	No	0.4084

rs6747755	2101036976	NPAS2	In	-	A/G	0.8452	No	0.2436
rs4851392	2101040494	NPAS2	In	-	A/G	0.8683	No	0.2987
rs1562313	2101045973	NPAS2	Ex	Y353Y	A/G	0.6300	No	0.1786
rs2305160	2101049822	NPAS2	Ex	T394A	C/T	0.2326	No	0.3373
rs2278728	2101056830	NPAS2	In	-	A/G	0.6926	No	0.2729
rs6719437	2101057589	NPAS2	In	-	A/G	0.7838	No	0.3385
rs6719533	2101057605	NPAS2	In	-	A/G	0.8246	No	0.4377
rs3754677	2101057812	NPAS2	In	-	C/T	0.0000	No	----
rs11123857	2101062330	NPAS2	In	-	A/G	0.1471	No	0.3211
rs1867861	2101066559	NPAS2	In	-	C/G	0.5511	No	0.4367
rs12712088	2101069110	RPL31	Prom	-	C/G	0.7436	No	0.5386
rs3739008	2101071086	RPL31	Prom	-	C/T	----	----	----
rs1053096	2101071133	RPL31	Prom	-	C/T	0.5782	No	0.2939
rs935401	2101071927	RPL31	Prom	-	A/T	0.5042	No	0.4053
rs13417456	2101073658	RPL31	Prom	-	C/T	0.3939	No	0.3012
rs9308843	2101076737	RPL31	Prom	-	A/G	0.3331	No	0.4830
rs935420	2238928251	HES6	3'UTR	-	C/G	0.1978	No	0.2837
rs7603349	2238951465	PER2	In(boundary)	-	A/G	.	Yes	0.0000
rs2304674	2238963904	PER2	In(boundary)	-	C/T	0.5739	No	0.2743
rs2340885	2238966390	PER2	Ex	V148M	A/G	.	Yes	0.0000
rs10462023	2238966581	PER2	In(boundary)	-	A/G	0.8787	No	0.2888
rs4663302	2238985761	PER2	Prom	-	C/T	0.4321	No	0.3489
rs3205438	3004999845	BHLHB2	Exon	D238G	A/G	.	Yes	0.0000
rs1467159	3005004562	BHLHB2	3'UTR	-	C/T	0.0433	No	0.4342
rs11706165	3005007236	BHLHB2	3'UTR	-	A/G	0.2790	No	0.4350
rs6442927	3005011346	BHLHB2	3'UTR	-	C/G	0.8596	No	0.2309
rs11732723	4056131486	TPARL	In	-	C/T	0.2137	No	0.4702
rs1056478	4056160217	CLOCK	Ex	E380K	C/T	----	----	----
rs11932595	4056164525	CLOCK	In	-	A/G	0.5062	No	0.4601
rs11133391	4056208883	CLOCK	In	-	C/T	0.1317	No	0.3574
rs12649507	4056221412	CLOCK	In	-	A/G	0.4480	No	0.3171
rs6850524	4056222925	CLOCK	In	-	C/G	0.7761	No	0.4034
rs9312662	4056227299	CLOCK	In	-	C/T	0.8896	No	0.3264
rs7665846	4056280173	PDCL2	In	-	C/T	----	----	----
rs2803547	10088398966	OPN4	Prom	-	C/T	0.9998	No	0.2743
rs2736689	10088403412	OPN4	Prom	-	A/C	0.5829	No	0.4138
rs10788521	10088407704	OPN4	In(boundary)	-	C/T	0.7662	No	0.3410
rs1079610	10088412096	OPN4	Ex	T394I	C/T	0.7558	No	0.2904
rs6584499	10104178249	CUEDC2	In	-	G/T	0.0123	No	0.3574
rs1409312	10104181790	CUEDC2	In	-	A/G	0.9876	No	0.2038
rs11022753	11013267430	ARNTL	In	-	C/T	0.4217	No	0.2485
rs7950226	11013274715	ARNTL	In	-	A/G	0.5626	No	0.4058
rs7938307	11013277102	ARNTL	In	-	A/C	0.2617	No	0.2924
rs4757144	11013287802	ARNTL	In	-	A/G	0.6206	No	0.4009
rs6486121	11013312346	ARNTL	In	-	C/T	0.6900	No	0.3458
rs6486122	11013318100	ARNTL	In	-	C/T	0.7326	No	0.3137
rs12421530	11013323298	ARNTL	In	-	C/G	0.7634	No	0.3529
rs3816360	11013324326	ARNTL	In	-	A/G	0.8595	No	0.3129
rs2290037	11013336549	ARNTL	In(boundary)	-	C/T	0.9974	No	0.0557
rs11022778	11013347436	ARNTL	In	-	G/T	0.2691	No	0.3452
rs11600996	11013352742	ARNTL	In	-	C/T	0.5722	No	0.4757

rs2278749	11013354454	ARNTL	In	-	A/G	0.3773	No	0.1294
rs969486	11013359711	GMRP-1	3'UTR	-	C/T	0.3207	No	0.3412
rs11038689	11045830840	CRY2	In	-	A/G	0.2499	No	0.2887
rs2863712	11045847765	CRY2	Ex	W339G	G/T	0.0000	No	----
rs2902545	11045847768	CRY2	Ex	D340Y	G/T	.	Yes	0.0000
rs7933420	11045853373	CRY2	In	-	A/T	0.9011	No	0.4536
rs11038699	11045853653	CRY2	In	-	A/G	0.6261	No	0.3246
rs2292910	11045860189	MAPK8IP1	Prom	-	A/C	0.7793	No	0.3871
rs3824872	11045862181	MAPK8IP1	Prom	-	G/T	0.0001	No	----
rs7938406	11112328005	NCAM1	Prom	-	C/T	0.5201	No	0.3796
rs4937870	11112331919	NCAM1	Prom	-	A/G	----	----	----
rs2212450	11112332077	NCAM1	Prom	-	A/G	----	----	----
rs1884	11112385807	NCAM1	In	-	C/G	0.2437	No	0.3636
rs11214476	11112450243	NCAM1	In	-	C/T	0.3547	No	0.1816
rs10891506	11112479293	NCAM1	In	-	C/G	0.8887	No	0.3125
rs2011487	11112493325	NCAM1	In	-	G/T	0.1603	No	0.4984
rs10891510	11112513370	NCAM1	In	-	G/T	0.1396	No	0.4602
rs1245138	11112513580	NCAM1	In	-	G/T	0.0824	No	0.3203
rs981555	11112548257	NCAM1	In	-	A/G	0.8344	No	0.2194
rs2574823	11112574923	NCAM1	In	-	C/G	0.0875	No	0.4082
rs1836796	11112578570	NCAM1	In	-	A/C	0.9130	No	0.4985
rs7122359	11112587758	NCAM1	In	-	G/T	0.8206	No	0.1536
rs686050	11112590454	NCAM1	In(boundary)	-	C/G	0.4892	No	0.3742
rs2850303	11112596440	NCAM1	In	-	C/T	0.4265	No	0.3993
rs9736945	11112605838	NCAM1	In	-	A/G	----	----	----
rs4646982	11112610615	NCAM1	In	-	A/C	0.1791	No	0.3416
rs646558	11112611117	NCAM1	In(boundary)	-	G/T	0.6800	No	0.1753
rs12785741	11112613597	NCAM1	In	-	C/G	0.4303	No	0.2508
rs12271908	11112615046	NCAM1	In	-	C/T	----	----	----
rs2303377	11112616711	NCAM1	In	-	C/T	0.0194	No	0.4056
rs2303378	11112616875	NCAM1	In	-	A/G	0.6815	No	0.1992
rs589760	11112621244	NCAM1	In	-	C/G	0.4181	No	0.3856
rs7130671	11112621581	NCAM1	In	-	C/T	0.0000	No	----
rs12794326	11112624066	NCAM1	In	-	C/T	0.8649	No	0.4953
rs3781878	11112625422	NCAM1	In	-	A/G	0.8308	No	0.2175
rs625087	11112629642	NCAM1	In	-	A/G	0.7743	No	0.2997
rs605843	11112630444	NCAM1	In	-	A/G	0.2932	No	0.2132
rs2298703	11112639815	NCAM1	In	-	C/T	0.1500	No	0.1506
rs17598303	11112641290	NCAM1	In	-	C/T	0.4237	No	0.1667
rs674246	11112646894	NCAM1	In	-	A/G	0.3032	No	0.2538
rs2156485	11112648767	NCAM1	In	-	A/G	0.4165	No	0.2253
rs10891527	11112657000	NCAM1	3'UTR	-	C/T	0.5701	No	0.1418
rs593217	11112658699	NCAM1	3'UTR	-	A/G	0.0341	No	0.4161
rs688011	11112659380	NCAM1	3'UTR	-	C/T	0.1204	No	0.2273
rs4963954	12026157898	BHLHB3	3'UTR	-	C/T	0.5570	No	0.3349
rs2343072	12026160314	BHLHB3	3'UTR	-	A/T	0.5250	No	0.2241
rs1048155	12026164355	BHLHB3	Exon	-	C/G	0.6126	No	0.4443
rs1057206	12026166577	BHLHB3	Ex	A380S	A/C	.	Yes	0.0000
rs3809140	12026169711	BHLHB3	Prom	-	C/T	----	----	----
rs10431216	12026171981	BHLHB3	Prom	-	C/G	0.3127	No	0.2318
rs10783783	12055088779	TIMELESS	3'UTR	-	A/G	0.1996	No	0.3833

rs2638290	12055100873	TIMELESS	Ex	E1034Q	C/G	.	Yes	0.0000
rs2291739	12055100920	TIMELESS	Ex	P1018L	C/T	0.0205	No	0.4954
rs2291738	12055101548	TIMELESS	In(boundary)	-	A/G	0.4210	No	0.4277
rs774047	12055102189	TIMELESS	Ex	R831Q	C/T	0.2050	No	0.4970
rs7302060	12055115359	TIMELESS	In	-	C/T	0.1715	No	0.4599
rs11610921	12055120140	TIMELESS	In	-	A/G	0.4133	No	0.4811
rs4640029	12105881191	LOC80298	In	-	A/T	0.3791	No	0.4350
rs714359	12105881312	LOC80298	In(boundary)	-	A/G	0.7850	No	0.2402
rs2287162	12105883372	LOC80298	Exon	-	C/G	0.9926	No	0.3036
rs2287161	12105883607	LOC80298	Prom	-	C/G	0.6261	No	0.4878
rs10861683	12105884027	LOC80298	Prom	-	A/T	0.5964	No	0.3420
rs11113153	12105884237	LOC80298	Prom	-	C/T	----	----	----
rs1861591	12105919394	CRY1	In	-	A/G	----	----	----
rs2585408	17007984478	PER1	3'UTR	-	C/T	0.0539	No	0.4149
rs11658069	17007987832	PER1	Ex	A850D	G/T	.	Yes	0.0000
rs2289591	17007988735	PER1	In(boundary)	-	G/T	0.0142	No	0.2160
rs3027190	17007988869	PER1	Ex	S796C	A/T	.	Yes	0.0000
rs3027189	17007988884	PER1	Ex	E791K	A/G	.	Yes	0.0000
rs2253820	17007988894	PER1	Ex	T787T	A/G	0.7746	No	0.1905
rs3027184	17007990742	PER1	Ex	S601F	C/T	.	Yes	0.0000
rs3027183	17007991050	PER1	In(boundary)	-	C/T	.	Yes	0.0000
rs2735609	17007992679	PER1	In(boundary)	-	G/T	.	Yes	0.0000
rs3027180	17007993338	PER1	Ex	D290G	A/G	.	Yes	0.0000
rs3027179	17007993792	PER1	In(boundary)	-	C/T	.	Yes	0.0000
rs3027177	17007993859	PER1	Ex	M197T	C/T	.	Yes	0.0000
rs2278637	17008002827	VAMP2	3'UTR	-	G/T	0.1698	No	0.2988
rs2102928	17035506754	NR1D1	In(boundary)	-	C/T	0.7446	No	0.3211
rs2071427	17035508018	NR1D1	In	-	A/G	0.9683	No	0.2948
rs2269457	17035508215	NR1D1	In	-	A/G	0.2575	No	0.2101
rs12941497	17035509120	NR1D1	In	-	A/G	0.6748	No	0.2553
rs939347	17035510219	NR1D1	Ex	-	A/G	0.5642	No	0.2307
rs2071570	17035510616	NR1D1	Prom	-	G/T	0.2235	No	0.2141
rs4996483	17077800084	CSNK1D	Ex	D385Y	A/C	0.9775	No	0.0016
rs12601586	17077807487	CSNK1D	In	-	A/G	----	----	----
rs7209167	17077823922	CSNK1D	In	-	C/G	0.5793	No	0.4045
rs3760780	19011550158	ACP5	Prom	-	A/G	0.7092	No	0.4367
rs386551	19053830098	DBP	In	-	C/G	0.9381	No	0.2826
rs135745	22037008137	CSNK1E	3'UTR	-	C/G	0.6725	No	0.4576
rs11548926	22037019319	CSNK1E	Ex	Y286C	A/G	----	----	----
rs135757	22037028153	CSNK1E	In	-	A/G	0.3371	No	0.2368
rs1997644	22037039722	CSNK1E	Prom	-	A/G	0.4443	No	0.4909
rs5757037	22037043689	CSNK1E	Prom	-	A/G	0.9517	No	0.3915
rs5757055	22037065353	.	.	.	C/G	0.6633	No	0.4542
rs6001098	22037067802	.	.	.	C/G	0.5576	No	0.3480
rs5757058	22037074425	.	.	.	A/T	0.2678	No	0.4277
rs3876032	22037085500	.	.	.	A/G	0.2982	No	0.0552
rs138368	22037115028	.	.	.	C/T	----	----	----
rs138383	22037124361	.	.	.	C/T	0.3192	No	0.4667

Figure S1. Partial view of one haplotype block of the CLOCK gene (software Haploview). First and last markers of the block are in strong LD with all intermediate markers, but the intermediate markers are not necessarily in LD with each other (solid spine method). rs11932595 (empty arrow) and rs12649507 (filled arrow) locations are indicated above the triangle plot. Each diamond represents the magnitude of historical LD of a single pair of markers from red ($D' > 0.80$) to white (absent LD). The green lines underline the LD diamonds belonging to these SNPs versus intermediate markers of this haplotype block.

Table S3. List of variants co-segregating ($r^2 > 0.80$) with rs12649507

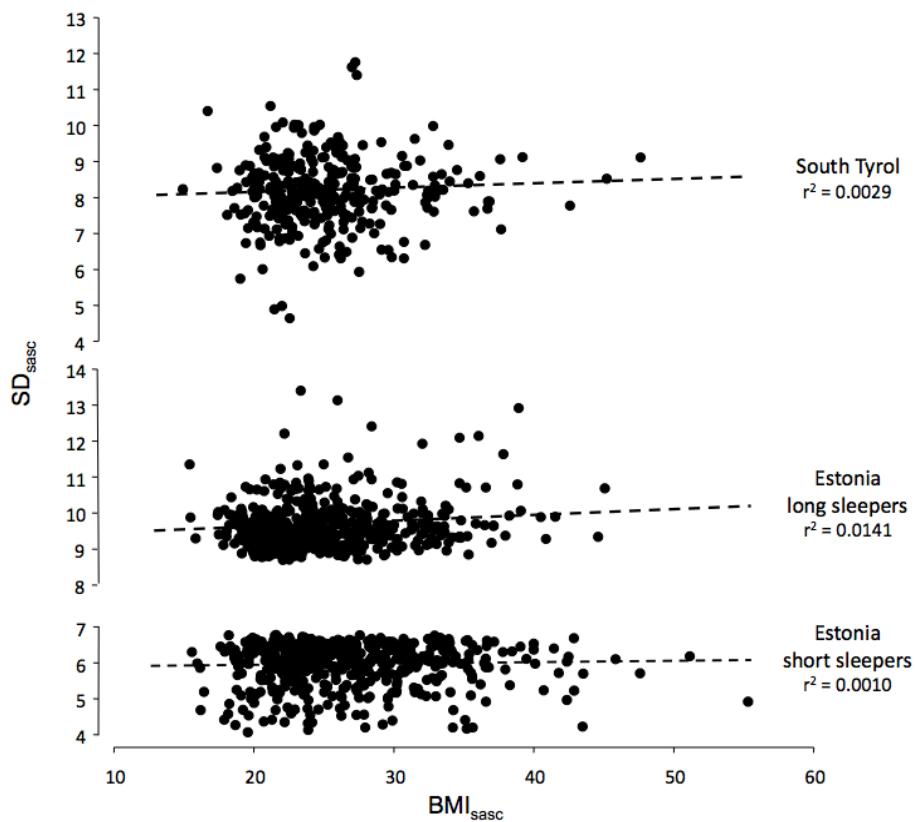| SNP	Tagging SNPs at $r^2 > 0.80$
rs12649507	rs6849474, rs4864996, rs2412648, rs12500686, rs6843722, rs12504300, rs11133389, rs12502813, rs4864543, rs7658446, rs12648271, rs13124436, rs12649507, rs13132420, rs13140173, rs2035691, rs13116035, rs2171618 and rs11943206

Figure S2. In the South Tyrolean and Estonian samples sleep duration is independent of BMI. Normalized averaged weekly sleep duration (SDasc) is plotted against normalized BMI (BMIasc) for the South Tyrolean sample, as well as for the Estonians with long and short sleep duration. For details see main text.