

## Supplemental text

### “Genetic variants in RBFOX3 are associated with sleep latency”

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*1. Study Populations (Stage 1/GWAS cohorts):*

ERF: The Erasmus Rucphen Family study is a family based study that includes over 3,000 participants descending from 22 couples living in the Rucphen region in the 19<sup>th</sup> century. All living descendants of these couples and their spouses were invited to take part in the study. 1,700 individuals from this population were assessed for sleep latency. After strict quality control, and removing individuals on medications that could affect sleep patterns 940 were available for the analysis, of which 747 individuals (58% females) were used in the genome-wide analysis <sup>1</sup>. All participants provided written informed consent. The medical ethics committee of Erasmus MC constituted according to the WMO (National Act Medical-scientific research in human beings) approved the Study (MEC 213.575/2002/114).

EGP/EGCUT: The Estonian Genome Center, University of Tartu (EGCUT) is a bio-bank consisting of data of 40,000 individuals from a population based Estonian cohort aged 18 years and older (67% females) <sup>2</sup>. For the current study, GWAS was performed on 933 subjects where both the Illumina HumanCNV370 genotype (array according to Illumina protocol in Estonian Biocenter Genotyping Core Facility) and the MCTQ questionnaire data were available. The cohort consisted of two sets of samples: 1) 534 population based samples which are part of a larger study and were selected randomly all over the country <sup>3</sup> and 2) 409 individuals selected as tails from the corrected chronotype distribution of 5,098 individuals. The age range was 18-86 years (mean age = 39.8 years; SD = 16.1 years). The current sample consists of 412 males (mean age 38.4 (SD =16.2) years) and 521 females

(mean age = 41.0 years; SD = 15.9 years). All the study participants signed informed consents and the Research Ethics Committee of the University of Tartu approved the study.

**MICROS:** The Micro-isolates in South Tyrol Study (MICROS) study is part of the genomic health care program 'GenNova' and was carried out in three villages of the Val Venosta on the populations of Stelvio, Vallelunga and Martello. This study was an extensive survey carried out in South Tyrol (Italy) in the period 2001-2003. A complete description of the study is available elsewhere <sup>4</sup>. Briefly, study participants were volunteers from three isolated villages located in the Italian Alps, in a German-speaking region bordering with Austria and Switzerland. Information on the health status of participants was collected through a standardized questionnaire. Laboratory data were obtained from standard blood analyses. Genotyping was performed on just under 1,400. Both genotype and phenotype data were available for 696 individuals who were finally included in the analysis. All participants provided written informed consent. The ethics committee of the province of South Tyrol for MICROS approved the study.

**KORA:** The KORA research project has evolved from the WHO MONICA study (Monitoring of Trends and Determinants of Cardiovascular Disease). The KORA genome-wide association study was done using samples from the KORA S4 survey <sup>5</sup>, which is a population-based sample from the region of Augsburg, Southern Germany. Subjects were recruited between 1999-2002 independent from KORA S3, but using the same platform with the same standard operating procedures and based on the same population. KORA F4 is part of this sample (with a 10-year follow-up) where 1,814 subjects were genome-wide

genotyped. We have excluded subjects older than 65 years old. In total, 510 (51% females) individuals who passed phenotype and genotype quality control were included in the GWA analysis. All study participants provided written informed consents and Ethik-Kommission der Bayerischen Landesärztekammer approved the KORA study.

CROATIA-Korcula: The CROATIA-Korcula Study is a family-based, cross-sectional study on the Dalmatian island of Korcula. In total, 610 subjects (64% females) who passed phenotype and genotype quality control were used for the GWA analysis <sup>6</sup>. All participants provided written informed consents. The CROATIA studies were approved by committees of the Medical School, University of Zagreb (2001; ref 018057 and 2006; ref 04-1097-2006), the Multi-Centre Research Ethics Committee of the National Health Service UK (2001; MREC 01/0/71), and NHS Lothian (2011; REF 11/AL/0222).

NESDA: The Netherlands Study of Depression and Anxiety includes 1,763 unrelated cases with current or remitted major depressive disorder and healthy controls. For the present study 540 subjects without a current major depressive disorder who passed phenotype and quality control were used for the analysis. The average age of the included participants was 41.3 years (66% females) <sup>7</sup>. All study participants signed written informed consents and the study protocol was approved centrally by the Ethical Review Board of the VU University Medical Center and subsequently by local review boards of each participating center.

ORCADES: The Orkney Complex Disease Study is a family-based cross sectional genetic epidemiological study in the isolated Scottish Orkney Islands. Genetic diversity is

decreased compared to the mainland Scottish population, consistent with a high endogamy<sup>8</sup>. The current study included 206 individuals (55% females) that had both directly observed and imputed genotypes and were also assessed for sleep patterns with MCTQ questionnaire. All participants provided written informed consents. North of Scotland Research Ethics Committee approved the study.

## *2. Study Populations (Stage 2/Replication cohorts):*

ARIC: The Atherosclerosis Risk in Communities Study (ARIC), is a prospective epidemiologic study that was conducted in four U.S. communities. The ARIC study was designed to investigate the etiology and natural history of atherosclerosis and cardiovascular risk factors. The study recruited a community sample of middle aged and older adults (age: 45-64) with a total sample size of 15,792 participants. Study participants were re-examined every three years with the first screen (baseline) occurring in 1987-89, the second in 1990-92, the third in 1993-95, and the fourth and last exam was in 1996-98. Sleep was assessed using the Sleep Heart Health Study (SHHS) questionnaire. The subjective latency to sleep onset was based on the following question: How many minutes does it usually take you to fall asleep at bedtime? Sleep Heart Health Study was approved by the IRBs at Case Western Reserve University and Brigham and Women's Hospital. Written informed consents were obtained from all study participants and the study was approved by the institutional review board of each field center institutes and participants gave informed consent including consent for genetic testing. The ARIC site at Johns Hopkins University was approved by the Johns Hopkins University Institutional Review Board on Human Subjects Research.

CHS: CHS is a prospective population-based cohort study of risk factors for cardiovascular heart disease and stroke in adults over age 65. The original cohort of 5,201 men and women was recruited in 1989-1990 from a random sample of the Medicare eligibility list in four United States communities. CHS genotyped 3,980 participants free of cardiovascular disease at baseline with available DNA and consent to genetic testing. After exclusions for call rate < 95%, sex mismatch or discordance with prior genotyping, 3,291 self-identified white participants remained. Of these, 1,533 completed the Sleep Heart Health Study Sleep Habits Questionnaire. Sleep Heart Health Study was approved by the IRBs at Case Western Reserve University and Brigham and Women's Hospital. CHS was approved by approved by the University of Washington Human Subjects Committee and institutional review committees at each site (University of California, Davis; Johns Hopkins University; Wake Forest University School of Medicine; University of Pittsburgh), the subjects gave written informed consent, and those included in the present analysis consented to the use of their genetic information for the study.

EGCUT1: 5,949 subjects from the EGCUT cohort, who were not genotyped in the initial GWAS, were used for the replication study. The sample consisted of 50.5% females and 49.5% males; Sleep assessment was performed with MCTQ. All participants provided written informed consents and the Research Ethics Committee of the University of Tartu approved the study.

EGCUT2: 4,057 new subjects from EGCUT cohort were used for this replication. The sample consisted of a) 517 individuals (46.7% females), age range 18-84 years

( $38.05 \pm 15.54$ ) who were genotyped by Illumina HumanCNV370 chips and b) 3,540 individuals (52.68% females), age range 18-89 years ( $48.90 \pm 20.04$ ) who were genotyped by Illumina OmniExpress chips. Sleep parameters were assessed with MCTQ. All participants signed written informed consents and the Research Ethics Committee of the University of Tartu approved the study.

ERF\_ext: An extension of the ERF study mentioned earlier. This consisted of 143 individuals phenotyped for sleep latency with MCTQ (Table S4). Written informed consents were obtained from all study participants. The medical ethics committee of Erasmus MC constituted according to the WMO (National Act Medical-scientific research in human beings) approved the Study (MEC 213.575/2002/114).

FHS: The National Heart Lung and Blood Institute's Framingham Heart Study is a three generational, longitudinal population-based cohort originally recruited in 1948 amongst the residents of the town of Framingham, Massachusetts for the study of cardiovascular disease. In 1971, a second cohort composed of the children from the Original cohort and those children's spouses was recruited and in 2002 a Third Generation cohort was recruited amongst candidates who had at least one parent in the Offspring cohort. Genotyping was performed on all participants who gave informed consent for genetic analyses. Sleep data was collected from Framingham Offspring Cohort participants as part of the Sleep Heart Health Study Sleep Habits Questionnaire. Sleep Heart Health Study was approved by the IRBs at Case Western Reserve University and Brigham and Women's Hospital. Participants

signed written informed consents and Institutional Review Board of Boston University Medical Campus approved the study.

NTR: Netherlands Twin Registry. Participants from the NTR [1] indicated in a survey the number of minutes they needed to get to sleep, once they had gotten ready to go to sleep. For this analysis, we used the answer provided for the non-working day. All participants provided written informed consents and the study was approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam (IRB number IRB-2991 under Federal wide Assurance-3703; IRB/institute code 03-180).

MrOS: The MrOS study population consists of 5,994 community dwelling, ambulatory men aged 65 years or older from six communities in the United States (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA). Inclusion criteria were designed to provide a study cohort that is representative of the broad population of older men. The inclusion criteria were: (1) ability to walk without the assistance of another, (2) absence of bilateral hip replacements, (3) ability to provide self-reported data, (4) residence near a clinical site for the duration of the study, (5) absence of a medical condition that (in the judgment of the investigator) would result in imminent death, and (6) ability to understand and sign an informed consent. To qualify as an enrollee, the participant had to provide written informed consent, complete the self-administered questionnaire (SAQ), attend the clinic visit, and complete at least the anthropometric, DEXA, and vertebral X-ray procedures<sup>9,10</sup>. Sleep assessment was

performed using PSQI at the first sleep visit. All data were collected with written informed consent as approved by the review boards of the coordinating center (California Pacific Medical Center) and the participating institutions (Birmingham, AL; the Monongahela Valley near Pittsburgh, PA; Minneapolis, MN; Palo Alto, CA; San Diego, CA; and Portland, OR)

CROATIA-Split: The CROATIA-Split study is a population based cohort study of 416 individuals residing in the city of Split, Croatia. The sample consisted of 58.2% females and 41.8% males. All participants signed written informed consent and the CROATIA studies were approved by committees of the Medical School, University of Zagreb (2001; ref 018057 and 2006; ref 04-1097-2006), the Multi-Centre Research Ethics Committee of the National Health Service UK (2001; MREC 01/0/71), and NHS Lothian (2011; REF 11/AL/0222).

QIMR: Queensland Institute of Medical Research. Between 1980 and 1982 a Health and Lifestyle Questionnaire was administered by mail to 5,867 complete pairs of twins who had been registered with the Australian Twin Registry. Responses were received from a total of 7,616 individuals (2,746 males and 4,780 females) and they had a mean age of 34.5 (S.D. = 14.3). All study participants signed written informed consents and the QIMR Human Research Ethics Committee (HREC) approved the study protocol. A total of 2,323 individuals provided both phenotypic and genotype information for the study. Sleep Latency was assessed with the question “On WEEKDAYS, how long do you think it usually takes you to fall asleep from when you first try to go to sleep”.

RS: The Rotterdam Study comprises of three cohorts including Rotterdam Study-I (RS-I), Rotterdam Study-II (RS-II) and the Rotterdam Study-III (RS-III). RS-I is a prospective population-based cohort study of 7,983 residents aged 55 years and older living in Ommoord, a suburb of Rotterdam, the Netherlands <sup>11</sup>. RS-II is a prospective population-based cohort study of respectively 3,011 residents aged 55 years and older and RS-III is a prospective population-based cohort study of 3,932 residents aged 45 years and older <sup>12</sup>. Sleep assessment was performed using PSQI. All participants signed written informed consents and the study was approved by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands.

SOF: The Study of Osteoporotic Fractures (SOF) is a prospective multicenter study of risk factors for vertebral and non-vertebral fractures <sup>13</sup>. The cohort is comprised of 9,704 community – dwelling women 65 years old or older recruited from populations-based listings in four U.S. areas: Baltimore, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley, Pennsylvania. 99% women enrolled in the study were of European descent with African American women initially excluded from the study due to their low incidence of hip fractures. (A cohort of AA women was recruited at the 6<sup>th</sup> Visit.)

The inclusion criteria were: 1) 65 years or older, (2) ability to walk without the assistance of another, (3) absence of bilateral hip replacements, (4) ability to provide self-reported data, (5) residence near a clinical site for the duration of the study, (6) absence of a medical condition that (in the judgment of the investigator) would result in imminent death, and (7)

ability to understand and sign an informed consent. To qualify as an enrollee, the participant had to provide written informed consent, complete the self-administered questionnaire (SAQ), attend the clinic visit, and complete at least the anthropometric measures. The SOF study recruited only Women. The SOF participants were followed up every four months by postcard or telephone to ascertain the occurrence of falls, fractures and changes in address. To date, follow-up rates have exceeded 95% for vital status and fractures. All fractures are validated by x-ray reports or, in the case of most hip fractures, a review of pre-operative radiographs. Blood samples were collected in 6,795 women at their Year 2 exam (Visit 2) and with written consent for use of DNA in genetic studies. Of these, we have GWAS data on 3,625 participants of European descent. Sleep assessment was performed using PSQI at the eighth clinical visit. All data were collected with written informed consent as approved by the review boards of the coordinating center (California Pacific Medical Center) and the participating institutions (Baltimore, MD; Pittsburgh, PA; Minneapolis, MN; Portland, OR)

### *3. Study specific acknowledgments:*

ARIC: The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. Infrastructure was partly supported by Grant Number

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CHS: This CHS research was supported by NHLBI contracts N01-HC-85239, N01-HC-85079 through N01-HC-85086; N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, HHSN268201200036C and NHLBI grants HL080295, HL087652, HL105756 with additional contribution from NINDS. Additional support was provided through AG-023629, AG-15928, AG-20098, and AG-027058 from the NIA. See also <http://www.chs-nhlbi.org/pi.htm>. DNA handling and genotyping was supported in part by National Center of Advancing Translational Technologies CTSI grant UL1TR000124 and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

ERF: The genotyping for the ERF study was supported by EUROSPAN (European Special Populations Research Network) through the European Commission FP6 STRP grant (018947; LSHG-CT-2006-01947). The ERF study was further supported by grants from the Netherlands Organisation for Scientific Research (NWO), Erasmus MC, the Centre for Medical Systems Biology (CMSB1 and CMSB2) and the Netherlands Genomics Initiative (NGI) and also received funding from the European Community's Seventh Framework Programme (FP7/2007-2013)/grant agreement HEALTH-F4-2007-201413 by the European Commission under the programme “Quality of Life and Management of the Living Resources” of 5th Framework Programme (no. QLG2-CT-2002-01254). High-throughput analysis of the ERF data was supported by joint grant from Netherlands Organisation for

Scientific Research and the Russian Foundation for Basic Research (NWO-RFBR 047.017.043). Exome sequencing analysis in ERF was supported by the ZonMw grant (*project 91111025*).

FHS: This research was conducted using the Linux Clusters for Genetic Analysis (LinGA) computing resources at Boston University Medical Campus.

MICROS: In South Tyrol, the study was supported by the Ministry of Health and Department of Educational Assistance, University and Research of the Autonomous Province of Bolzano, and the South Tyrolean Sparkasse Foundation

MrOS: The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Center for Research Resources (NCRR), and NIH Roadmap for Medical Research under the following grant numbers: U01 AR45580, U01 AR45614, U01 AR45632, U01 AR45647, U01 AR45654, U01 AR45583, U01 AG18197, U01-AG027810, and UL1 RR024140. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) provides funding for the MrOS ancillary study ‘Replication of candidate gene associations and bone strength phenotype in MrOS’ under the grant number R01-AR051124. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) provides funding for the MrOS ancillary study ‘GWAS in MrOS and SOF’ under the grant

number RC2ARO58973. The National Heart, Lung, and Blood Institute (NHLBI) provides funding for the MrOS Sleep ancillary study "Outcomes of Sleep Disorders in Older Men" under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839.

NESDA: Funding was obtained from the Netherlands Organization for Scientific Research (Geestkracht program), the Center for Medical Systems Biology (CSMB, NWO Genomics), the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI -NL, 184.021.007), the VU University's Institute for Health and Care Research (EMGO+ ) and Neuroscience Campus Amsterdam (NCA), Genotyping was funded by the Genetic Association Information Network (GAIN) of the Foundation for the US National Institutes of Health, the (NIMH, MH081802).

NTR: Funding was obtained from ZonMW (31160008), the Center for Medical Systems Biology (CSMB, NWO Genomics), the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI -NL, 184.021.007), the VU University's Institute for Health and Care Research (EMGO+ ) and Neuroscience Campus Amsterdam (NCA), European Research Council (ERC-230374 and ERC-284167) Genotyping was funded from multiple grants, including the Genetic Association Information Network (GAIN) of the Foundation for the US National Institutes of Health, the (NIMH, MH081802), NWO (NWO/SPI 56-464-14192).

RS: The generation and management of GWAS genotype data for the Rotterdam Study is supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) project nr. 050-060-810. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. Bundesministerium fuer Forschung und Technology; grants 01 AK 803 A-H, 01 IG 07015 G.

SOF: The Study of Osteoporotic Fractures (SOF) is supported by National Institutes of Health funding. The National Institute on Aging (NIA) provides support under the following grant numbers: R01 AG005407, R01 AR35582, R01 AR35583, R01 AR35584, R01 AG005394, R01 AG027574, R01 AG027576, and R01 AG026720.

CROATIA-Split: The CROATIA-Split study was supported through the grants from the Medical Research Council UK.;and Ministry of Science, Education and Sport of the Republic of Croatia. (number 108-1080315-0302). The SNP genotyping for the CROATIA-Split cohort was performed by AROS Applied Biotechnology, Aarhus, Denmark.

#### *4. Ethical statement:*

Written informed consent was obtained from all study participants and an appropriate local committee approved study protocols.

ERF: All participants provided written informed consent. The medical ethics committee of Erasmus MC constituted according to the WMO (National Act Medical-scientific research in human beings) approved the Study (MEC 213.575/2002/114).

EGP/EGCUT: All the study participants signed informed consent and the Research Ethics Committee of the University of Tartu approved the study.

MICROS: All participants provided written informed consent. The ethics committee of the province of South Tyrol for MICROS approved the study.

KORA: All study participants provided written informed consent and Ethik-Kommission der Bayerischen Landesärztekammer approved the KORA study.

CROATIA (Korcula/SPLIT): All participants provided written informed consent. The CROATIA studies were approved by committees of the Medical School, University of Zagreb (2001; ref 018057 and 2006; ref 04-1097-2006), the Multi-Centre Research Ethics Committee of the National Health Service UK (2001; MREC 01/0/71), and NHS Lothian (2011; REF 11/AL/0222).

NESDA: All study participants signed written informed consent and the study protocol was approved centrally by the Ethical Review Board of the VU University Medical Center and subsequently by local review boards of each participating center.

ORCADES: All participants provided written informed consent. North of Scotland Research Ethics Committee approved the study.

ARIC: Written informed consents were obtained from all study participants and the study was approved by the institutional review board of each field center institutes and participants gave informed consent including consent for genetic testing. The ARIC site at Johns Hopkins University was approved by the Johns Hopkins University Institutional Review Board on Human Subjects Research.

CHS: was approved by approved by the University of Washington Human Subjects Committee and institutional review committees at each site (University of California, Davis; Johns Hopkins University; Wake Forest University School of Medicine; University of Pittsburgh), the subjects gave written informed consent, and those included in the present analysis consented to the use of their genetic information for the study.

FHS: Participants signed written informed consent and the study was approved by Institutional Review Board of Boston University Medical Campus.

NTR: All participants provided written informed consent and the study was approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam (IRB number IRB-2991 under Federal wide Assurance-3703; IRB/institute code 03-180).

MROS & SOF: All participants in this study provided written informed consent and the review boards of the coordinating center (California Pacific Medical Center) and the participating institutions (Birmingham, AL; the Monongahela Valley near Pittsburgh, PA; Minneapolis, MN; Palo Alto, CA; San Diego, CA; and Portland, OR) approved the studies.

QIMR: All study participants signed written informed consent and the QIMR Human Research Ethics Committee (HREC) approved the study protocol.

RS: All participants provided written informed consent and the study was approved by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands.

## References:

- 1 Aulchenko YS, Heutink P, Mackay I *et al.* Linkage disequilibrium in young genetically isolated Dutch population. *Eur J Hum Genet* 2004; **12**: 527-534.
- 2 Metspalu A. The Estonian Genome Project. *Drug Dev Res* 2004; **62**: 97-101.
- 3 Nelis M, Esko T, Magi R *et al.* Genetic structure of Europeans: a view from the North-East. *PLoS One* 2009; **4**: e5472.
- 4 Pattaro C, Marroni F, Riegler A *et al.* The genetic study of three population microisolates in South Tyrol (MICROS): study design and epidemiological perspectives. *BMC Med Genet* 2007; **8**: 29.
- 5 Wichmann HE, Gieger C, Illig T, Group MKS. KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* 2005; **67 Suppl 1**: S26-30.
- 6 Polasek O, Marusic A, Rotim K *et al.* Genome-wide association study of anthropometric traits in Korcula Island, Croatia. *Croat Med J* 2009; **50**: 7-16.
- 7 Boomsma DI, Willemsen G, Sullivan PF *et al.* Genome-wide association of major depression: description of samples for the GAIN Major Depressive Disorder Study: NTR and NESDA biobank projects. *Eur J Hum Genet* 2008; **16**: 335-342.
- 8 McQuillan R, Leutenegger AL, Abdel-Rahman R *et al.* Runs of homozygosity in European populations. *Am J Hum Genet* 2008; **83**: 359-372.
- 9 Orwoll E, Blank JB, Barrett-Connor E *et al.* Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study--a large observational study of the determinants of fracture in older men. *Contemp Clin Trials* 2005; **26**: 569-585.

- 10 Blank JB, Cawthon PM, Carrion-Petersen ML *et al.* Overview of recruitment for the osteoporotic fractures in men study (MrOS). *Contemp Clin Trials* 2005; **26**: 557-568.
- 11 Hofman A, Breteler MM, van Duijn CM *et al.* The Rotterdam Study: objectives and design update. *Eur J Epidemiol* 2007; **22**: 819-829.
- 12 Hofman A, van Duijn CM, Franco OH *et al.* The Rotterdam Study: 2012 objectives and design update. *Eur J Epidemiol* 2011; **26**: 657-686.
- 13 Cummings SR, Nevitt MC, Browner WS *et al.* Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995; **332**: 767-773.

**Table S1: Descriptive Statistics of stage1 (discovery) and stage2 (replication) cohorts**

Population	Sample	Average sleep latency, minutes (sd)	Average [LN(sleep latency (minutes) + c)](sd)	Average age, years (sd)
<i>Stage 1 Meta-analysis cohort</i>				
<b>EGP</b>	Total	15.47(17.76)	2.31(1.02)	39.85(16.08)
	Male	14.38(15.74)	2.25(1.01)	38.38(16.24)
	Female	16.54(19.70)	2.37(1.04)	41.03(15.88)
<b>ERF</b>	Total	17.69(18.63)	2.56(0.85)	45.67(13.00)
	Male	15.53(14.99)	2.48(0.80)	47.42(12.98)
	Female	19.59(21.16)	2.64(0.88)	44.12(12.83)
<b>KORA</b>	Total	10.33 (9.72)	2.08(0.79)	54.29 (5.49)
	Male	8.71 (7.75)	1.95 (0.77)	54.64(5.66)
	Female	11.97 (11.16)	2.21 (0.81)	53.96 (5.32)
<b>CROATIA-Korcula</b>	Total	19.55(12.15)	2.56(1.02)	56.41(12.2)
	Male	17.58(13.86)	2.52(0.94)	57.61(12.97)
	Female	20.69(18.71)	2.59(1.07)	55.72(11.7)
<b>MICROS</b>	Total	13.31(14.29)	2.22(0.94)	40.26(14.52)
	Male	11.94(12.06)	2.16(0.89)	41.24(14.50)
	Female	14.50(15.88)	2.28(0.98)	39.44(14.53)
<b>NESDA</b>	Total	18.52 (18.52)	2.60 (0.90)	41.25 (12.26)
	Male	16.63 (16.95)	2.52 (0.85)	44.15 (12.40)
	Female	19.49 (19.22)	2.64 (0.93)	39.77 (11.94)
<b>ORCADES</b>	Total	15.95(15.61)	2.36(1.00)	51.08(11.08)
	Male	12.67(11.26)	2.22(0.89)	51.08(13.18)
	Female	18.67(18.2)	2.47(1.08)	51.26(13.85)
<i>Stage 2 Replication cohort</i>				
<b>ARIC</b>	Total	17.49(18.80)	2.55(0.81)	62.53(5.65)
	Male	15.07(16.38)	2.43(0.78)	63.11(5.65)
	Female	19.57(20.42)	2.66(0.82)	62.03(5.59)
<b>CHS</b>	Total	20.70(20.57)	2.71(0.85)	77.89(4.66)
	Male	17.39(16.34)	2.58(0.80)	78.29(4.84)
	Female	22.78(22.58)	2.79(0.87)	77.63(4.52)
<b>FHS</b>	Total	15.11 (14.68)	2.39 (0.82)	58.80 (9.47)
	Male	14.17 (13.25)	2.36 (0.78)	58.94 (9.41)
	Female	15.99 (15.86)	2.43 (0.85)	58.66 (9.52)
<b>EGCUT1</b>	Total	12.45(12.85)	2.13(1.02)	36.45(10.70)
	Male	12.15(12.57)	2.12(0.99)	33.78(11.18)
	Female	12.75(13.12)	2.14(1.05)	39.06(9.50)
<b>EGCUT2</b>	Total	16.09(17.21)	2.37(1.03)	47.51(19.85)
	Male	14.81(16.06)	2.30(1.01)	46.98(19.32)
	Female	17.28(18.14)	2.43(1.05)	48.01(20.32)
<b>ERF_ext</b>	Total	17.43(17.13)	2.55(0.91)	49.19(13.07)
	Male	16.33(13.91)	2.53(0.85)	51.24(11.87)
	Female	18.59(19.97)	2.58(0.91)	47.05(13.98)
<b>MrOS</b>	Total	16.26(15.87)	2.55 (0.73)	76.62 (5.69)
	Male	16.26(15.87)	2.55 (0.73)	76.62 (5.69)
	Female	NA	NA	NA
<b>NTR</b>	Total	14.16 (15.19)	1.00 (0.40)	50.57 (14.10)
	Male	11.59 (11.72)	0.93 (0.39)	54.63 (13.58)
	Female	15.82 (16.86)	1.04 (0.40)	47.94 (13.82)
<b>RS-I</b>	Total	21.13(28.07)	2.58(0.92)	75.57 (6.08)
	Male	14.74(19.97)	2.32(0.81)	75.31(5.80)
	Female	26.30(32.32)	2.79(0.96)	75.79(6.29)
<b>RS-II</b>	Total	20.35(28.96)	2.52(0.93)	68.49(7.23)
	Male	14.67(19.90)	2.29(0.83)	68.54(6.68)
	Female	25.13(34.08)	2.70(0.97)	68.45(7.67)
<b>RS-III</b>	Total	17.61(25.13)	2.38(0.97)	55.87(5.62)
	Male	13.68(22.18)	2.13(0.95)	55.86(5.48)

<b>SOF</b>	Female	20.90(26.94)	2.59(0.93)	55.89(5.74)
	Total	23.00(23.77)	2.79(0.87)	84.20(3.69)
	Male	NA	NA	NA
	Female	23.00(23.77)	2.79(0.87)	84.20(3.69)
<b>CROATIA-Split</b>	Total	16.39(18.31)	2.30(1.06)	49.83(13.7)
	Male	13.13(13.34)	2.12(1.03)	48.96(14.50)
	Female	18.80(20.95)	2.43(1.07)	50.47(13.07)
	Total	20.98(22.94)	2.67(0.90)	31.28(10.88)
<b>QIMR</b>	Male	17.67(16.26)	2.56(0.86)	28.17(8.12)
	Female	22.14(24.78)	2.71 (0.92)	32.37(11.51)
	Total	20.98(22.94)	2.67(0.90)	31.28(10.88)
	Female	23.00(23.77)	2.79(0.87)	84.20(3.69)

**Table S2: Genotyping and quality control in the stage 1 (discovery) and stage 2 (replication) cohorts**

Abbreviations: MCTQ: Munich Chronotype Questionnaire; PSQI: Pittsburg Sleep Quality Index; SHHS: Sleep Heart Health Study Sleep Habits Questionnaire; JSHQ: Johns' Sleep Habits Questionnaire

Study sample	Origin	Sample type	Sample size (%women)	Sleep assessment	Genotyping Platform	Quality control of genotyped SNPs				Genetic Imputations software used	Build	Analysis software used
						HWE p-value	SNP call rate	Sample call rate	MAF			
Stage 1 Meta-analysis cohort												
EGP	Estonian	Population based	933(56)	MCTQ	Illumina 370K	10 <sup>-6</sup>	98%	95%	0.01	MACH	36	ProbABEL
ERF	Dutch	isolate	747(58)	MCTQ	Illumina 6K, 318K, 370K, Affymetix 250K	10 <sup>-6</sup>	95%	95%	0.01	MACH	36	ProbABEL
KORA	German	Population based	510(51)	MCTQ	Affymetrix 1000K	10 <sup>-5</sup>	95%	95%	0.01	MACH	36	ProbABEL
CROATIA-Korcula	Croatian	isolate	610(64)	MCTQ	Illumina 370K	10 <sup>-10</sup>	98%	98%	0.02	MACH	36	ProbABEL
MICROS	German	isolate	696(57)	MCTQ	Illumina 300K	10 <sup>-6</sup>	98%	98%	0.01	MACH	36	ProbABEL
NESDA	Dutch	Population based	540(66)	MCTQ	Perlegen 600K	-	95%	95%	0.01	IMPUTE	35	SNPTEST
ORCADES	Scottish	isolate	206(55)	MCTQ	Illumina 318K	10 <sup>-10</sup>	98%	98%	0.02	MACH	36	ProbABEL
Stage 2 Replication cohort												
ARIC	European-Americans	Population based	3583(54)	SHHS	Affymetrix 6.0	NA	NA	NA	NA	MACH version 1.0.16	36	ProbABEL, PLINK, R
CHS	European-Americans	Population based	1533(62)	SHHS	Illumina 370 CNV	10 <sup>-5</sup>	97%	95%	0.01	BimBamv0.99	36	R

<b>EGCUT1</b>	Estonian	Population based	5925(51)	MCTQ	TAQMAN	NA	NA	NA	NA	NA	NA	PLINK
<b>EGCUT2</b>	Estonian	Population based	4057(52)	MCTQ	Illumina370K, HumanOmniExpress	10 <sup>-6</sup>	95%	98%	0.01	IMPUTEv2	36	SNPTEST2
<b>ERF_ext</b>	Dutch	Family based	143(49)	MCTQ	Illumina 370K, 610K	10 <sup>-6</sup>	98%	98%	10 <sup>-8</sup>	MACH	36	SOLAR
<b>FHS</b>	European	Family based	2192(52)	SHHS	Affymetrix 500K and MIPS 50K combined	10 <sup>-6</sup>	97%	97%	0.01	MACH 1.00.15	36	LMEKIN package R
<b>MrOS</b>	European Americans	Population based	1849(0)	PSQI	Illumina HumanOmni1_Quad	10 <sup>-4</sup>	97%	97%	0.01	minimac	36	R
<b>NTR</b>	Dutch	Population based	1795(61)	MCTQ	Affymetrix 6.0, perlegen 5.0, Illumina 370K, 660K, Omni Express 1M	10 <sup>-5</sup>	95%	NA	0.01	IMPUTEv2	36	SPSS
<b>RS-I</b>	Dutch	Population based	2334(55)	PSQI	Illumina 550K	10 <sup>-6</sup>	97.5%	98%	0.01	MACH	36	SPSS
<b>RS-II</b>	Dutch	Population based	1403(54)	PSQI	Illumina 550K	10 <sup>-6</sup>	97.5%	98%	0.01	MACH	36	SPSS
<b>RS-III</b>	Dutch	Population based	1904(54)	PSQI	Illumina 550K	10 <sup>-6</sup>	97.5%	98%	0.01	MACH	36	GRIMP
<b>SOF</b>	European Americans	Population based	1480(100)	PSQI	Illumina HumanOmni1_Quad	10 <sup>-4</sup>	97%	97%	0.01	minimac	36	R
<b>CROATIA-Split</b>	Croatian	Isolate	416(58)	MCTQ	Illumina 370NV	10 <sup>-6</sup>	98%	97%	0.01	MACH	36	ProbABEL
<b>QIMR</b>	Australian	Family Based	2280(73)	JSHQ	Illumina 317K, Illumina 370K, Illumina 610K	10 <sup>-5</sup>	95%	98%	0.01	MACH	36	Merlin-offline

**Table S3: Pharmacological sleep agents. Drug groups and correspondent ATC codes used as exclusion criteria when selecting phenotyped subjects for the independent GWA studies**

Drug groups	Pharmacological ATC codes
<b>Benzodiazepines</b>	N05CD, N05CF
<b>Barbiturates</b>	N01AF, N01AG, N03AA, N05CA, N05CB, N05CX
<b>Imipramine</b>	N06AA02, N06AA03, N06AA06
<b>Nortriptyline</b>	N06AA10
<b>Neuroleptics</b>	N05AK
<b>Phenothiazines</b>	N05AB, N05AC, N05AA
<b>Fluoxetine</b>	N06AB03
<b>Sertraline</b>	N06AB06
<b>Paroxetine</b>	N06AB05
<b>β-Blockers, propranolol</b>	C07, S01ED
<b>Theophylline</b>	R03DA04
<b>Amphetamine</b>	N06B

**Table S4: Summary of replicated SNPs in the replication cohorts**

Cohort	SNP	Genotyped/imputed	MAF	Call rate	Imputation quality
ARIC	rs9900428	Imputed	0.30	NA	0.966
	rs9907432	Imputed	0.31	NA	0.979
	rs7211029	Genotyped	0.31	1	NA
CHS	rs9900428	Imputed	0.27	NA	0.708
	rs9907432	Imputed	0.28	NA	0.722
	rs7211029	Imputed	0.28	NA	0.721
EGCUT1	rs9900428	No TaqMAN assay	NA	NA	NA
	rs9907432	Genotyped	0.28	0.988	NA
	rs7211029	Genotyped	0.28	0.983	NA
EGCUT2	rs9900428	Imputed	0.28	NA	0.983
	rs9907432	Genotyped	0.28	1	NA
	rs7211029	Imputed	0.28	NA	0.991
ERF_ext	rs9900428	Imputed	0.25	NA	0.945
	rs9907432	Imputed	0.26	NA	0.995
	rs7211029	Imputed	0.33	NA	0.806
FHS	rs9900428	Imputed	0.27	NA	NA
	rs9907432	Imputed	0.28	NA	NA
	rs7211029	Imputed	0.28	NA	NA
MrOS	rs9900428	Imputed	0.27	NA	0.985
	rs9907432	Genotyped	0.28	0.99	NA
	rs7211029	Imputed	0.28	NA	0.999
NTR	rs9900428	Imputed	0.30	NA	0.963
	rs9907432	Imputed	0.30	NA	0.979
	rs7211029	Imputed	0.25	NA	0.599
RS-I	rs9900428	Imputed	0.31	NA	0.986
	rs9907432	Genotyped	0.32	0.999	0.999
	rs7211029	Imputed	0.32	NA	0.997
RS-II	rs9900428	Imputed	0.30	NA	0.984
	rs9907432	Genotyped	0.31	0.992	0.999
	rs7211029	Imputed	0.31	NA	0.998
RS-III	rs9900428	Imputed	0.31	NA	0.984
	rs9907432	Imputed	0.32	NA	0.999
	rs7211029	Imputed	0.32	NA	0.998
SOF	rs9900428	Imputed	0.30	NA	0.985
	rs9907432	Genotyped	0.30	0.99	NA
	rs7211029	Imputed	0.30	NA	0.999
CROATIA-Split	rs9900428	Imputed	0.25	NA	0.986
	rs9907432	Genotyped	0.25	0.997	0.999
	rs7211029	Imputed	0.25	NA	0.995
QIMR	rs9900428	Imputed	0.30	NA	0.973
	rs9907432	Genotyped	0.31	0.991	NA
	rs7211029	Imputed	0.31	NA	0.991

**Table S5: Results of Biological process prediction of *RBFOX3* based on Gene Ontology**

Gene Ontology Biological Process	P_value	Z_score
Synaptic vesicle exocytosis	7.24E-17	8.343
Regulation of synaptic plasticity	6.34E-16	8.0826
Membrane depolarization	1.02E-11	6.8034
Regulation of excitatory postsynaptic membrane potential	3.05E-11	6.64429
Regulation of synaptic transmission	9.43E-11	6.47578
Gamma-aminobutyric acid signaling pathway	1.88E-10	6.37048
Axonogenesis	1.95E-10	6.36552
Neurotransmitter secretion	3.12E-10	6.29252
Regulation of neuronal synaptic plasticity	3.86E-10	6.25952
Regulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate selective glutamate receptor activity	6.19E-10	6.1856
Regulation of neuron projection development	6.68E-10	6.17347
Behavioral fear response	7.27E-10	6.16009
Behavioral defense response	1.26E-09	6.07281
Regulation of postsynaptic membrane potential	2.47E-09	5.96361
Potassium ion transport	4.52E-09	5.86407
Long-term memory	5.48E-09	5.83205
Regulation of transmission of nerve impulse	5.66E-09	5.82637
Regulation of neurological system process	6.22E-09	5.81081
Neurotransmitter transport	1.02E-08	5.72781
Neuron-neuron synaptic transmission	1.08E-08	5.71811
Synaptic transmission, glutamatergic	1.09E-08	5.71556
Glutamate secretion	1.15E-08	5.70656
Adult walking behavior	2.19E-08	5.59643
Learning or memory	2.67E-08	5.56167
Regulation of dendrite development	2.86E-08	5.54988
Regulation of long-term neuronal synaptic plasticity	2.91E-08	5.54693
Regulation of neuron differentiation	3.78E-08	5.50086
Cognition	4.12E-08	5.48577
Calcium ion transmembrane transport	5.88E-08	5.42242
Synaptic vesicle transport	6.82E-08	5.39592
Regulation of axonogenesis	2.00E-07	5.19938
Cerebellum development	2.36E-07	5.16864
Adult locomotory behavior	2.38E-07	5.16707
Regulation of neurogenesis	3.02E-07	5.12213
Cellular biogenic amine biosynthetic process	3.12E-07	-5.11583
Regulation of dendrite morphogenesis	3.64E-07	5.08668
Visual learning	3.89E-07	5.07419
Regulation of neurotransmitter levels	4.37E-07	5.05216
Learning	5.03E-07	5.02516
Calcium ion transport	5.55E-07	5.00629
Ion transmembrane transport	5.69E-07	5.00148
Dendrite morphogenesis	5.92E-07	4.9939
Diol biosynthetic process	6.42E-07	-4.97804
Catechol-containing compound biosynthetic process	6.42E-07	-4.97804
Catecholamine biosynthetic process	6.42E-07	-4.97804
Long-term synaptic potentiation	7.10E-07	4.95872
Cellular potassium ion transport	7.61E-07	4.94513
Potassium ion transmembrane transport	7.61E-07	4.94513
Regulation of nervous system development	7.91E-07	4.93768
Regulation of cell projection organization	9.52E-07	4.90135

**Table S6: Results of pathway analysis of *RBFOX3* based on BioCarta**

BioCarta	P_value	Z_score
Nitric Oxide Signaling Pathway	4.74E-14	7.539007
Ca++/ Calmodulin-dependent Protein Kinase Activation	1.12E-10	6.450057
Gamma-aminobutyric Acid Receptor Life Cycle	7.37E-09	5.782189
Regulation of ckl/cdk5 by type 1 glutamate receptors	1.36E-06	4.830675
Transcription factor CREB and its extracellular signals	7.28E-04	3.37887
Sonic Hedgehog (Shh) Pathway	0.001278	3.220773
Regulation of PGC-1a	0.001418	3.190999
Rac 1 cell motility signaling pathway	0.002164	3.066726
Stathmin and breast cancer resistance to antimicrotubule agents	0.003455	2.924029
Actions of Nitric Oxide in the Heart	0.004873	2.815317
Bioactive Peptide Induced Signaling Pathway	0.0075	2.673801
Endocytotic role of NDK, Phosphins and Dynamin	0.010267	2.566718
Role of MEF2D in T-cell Apoptosis	0.029301	2.179409
Effects of calcineurin in Keratinocyte Differentiation	0.029493	2.176834
Protein Kinase A at the Centrosome	0.032887	2.133462
Acetylation and Deacetylation of RelA in The Nucleus	0.034059	-2.11938
Repression of Pain Sensation by the Transcriptional Regulator DREAM	0.056322	1.908535
Telomeres, Telomerase, Cellular Aging, and Immortality	0.060684	-1.87579
Fc Epsilon Receptor I Signaling in Mast Cells	0.072693	1.794756
BCR Signaling Pathway	0.073281	1.791076
Corticosteroids and cardioprotection	0.078801	-1.75768
Links between Pyk2 and Map Kinases	0.088007	1.706007
Chaperones modulate interferon Signaling Pathway	0.092243	-1.68368
TNFR1 Signaling Pathway	0.093909	-1.67513
Bone Remodelling	0.096713	-1.661
Regulation of hematopoiesis by cytokines	0.105341	-1.6195
Apoptotic Signaling in Response to DNA Damage	0.118052	1.563002
HIV-I Nef: negative effector of Fas and TNF	0.118239	-1.56221
CCR3 signaling in Eosinophils	0.118771	1.559954
Angiotensin II mediated activation of JNK Pathway via Pyk2 dependent signaling	0.124033	1.538063
NF-kB Signaling Pathway	0.137832	-1.48391
NO2-dependent IL 12 Pathway in NK cells	0.138785	-1.48033
Adhesion and Diapedesis of Lymphocytes	0.140497	-1.47394
PDGF Signaling Pathway	0.145484	1.455671
Signaling Pathway from G-Protein Families	0.147786	1.447396
Attenuation of GPCR Signaling	0.163153	1.394546
Signal transduction through IL1R	0.167381	-1.38067
Thrombin signaling and protease-activated receptors	0.173938	1.359659
Ceramide Signaling Pathway	0.179669	-1.34178
Pertussis toxin-insensitive CCR5 Signaling in Macrophage	0.184728	1.326336
Signaling of Hepatocyte Growth Factor Receptor	0.187316	1.31856
Hypoxia and p53 in the Cardiovascular system	0.191816	-1.30522
TACI and BCMA stimulation of B cell immune responses.	0.192633	-1.30283
Erk1/Erk2 Mapk Signaling pathway	0.193686	-1.29975
T Helper Cell Surface Molecules	0.198135	-1.28688
Role of Parkin in the Ubiquitin-Proteasomal Pathway	0.198721	1.285204

**Table S7: Results of functional prediction of *RBFOX3* based on Reactome**

Reactome	P_value	Z_score
Dopamine Neurotransmitter Release Cycle	9.10E-19	8.845619228
Serotonin Neurotransmitter Release Cycle	9.10E-19	8.845619228
Neuronal System	2.25E-18	8.744010873
Glutamate Neurotransmitter Release Cycle	3.65E-15	7.866557523
CREB phosphorylation through the activation of CaMKII	6.86E-15	7.786977433
Depolarization of the Presynaptic Terminal Triggers the Opening of Calcium Channels	1.13E-13	7.424833029
Transmission across Chemical Synapses	3.91E-13	7.258802905
Ras activation upon Ca <sup>2+</sup> influx through NMDA receptor	1.04E-12	7.124991039
Acetylcholine Neurotransmitter Release Cycle	1.19E-11	6.78138084
GABA A receptor activation	2.96E-11	6.648787904
Post NMDA receptor activation events	2.28E-10	6.341510697
Potassium Channels	9.18E-10	6.123073899
CREB phosphorylation through the activation of Ras	2.41E-09	5.967496278
Unblocking of NMDA receptor, glutamate binding and activation	2.47E-09	5.963193857
Neurotransmitter Release Cycle	2.52E-09	5.959974009
Ligand-gated ion channel transport	3.90E-09	5.888539163
Norepinephrine Neurotransmitter Release Cycle	5.54E-09	5.830132075
Voltage gated Potassium channels	9.20E-09	5.744915769
Neurotransmitter Receptor Binding And Downstream Transmission In The Postsynaptic Cell	1.06E-08	5.720154385
Reduction of cytosolic Ca <sup>++</sup> levels	1.41E-08	5.672005547
Activation of NMDA receptor upon glutamate binding and postsynaptic events	6.45E-08	5.405961465
Botulinum neurotoxicity	9.54E-08	5.335184481
Ion channel transport	2.10E-07	5.190418891
Trafficking of AMPA receptors	7.09E-07	4.958815626
Glutamate Binding, Activation of AMPA Receptors and Synaptic Plasticity	7.09E-07	4.958815626
Platelet calcium homeostasis	1.28E-06	4.842971175
GABA synthesis, release, reuptake and degradation	2.18E-06	4.735521375
GABA receptor activation	3.92E-06	4.61545128
Amine-derived hormones	1.55E-05	-4.321445002
Class C/3 (Metabotropic glutamate/pheromone receptors)	2.90E-05	4.180959836
Proteolytic cleavage of SNARE complex proteins	3.51E-05	4.137487811
Interaction between L1 and Ankyrins	8.44E-05	3.931430808
cGMP effects	8.50E-05	3.92998016

**Table S8: Expression of *RBFOX3* in various tissues**

MeSH_name	number_of_samples	AUC	P_value
Cerebellum	36	0.994427506	9.68E-25
Frontal Lobe	62	0.992096278	5.40E-41
Cerebral Cortex	276	0.991547227	1.04E-174
Prefrontal Cortex	46	0.991028923	9.65E-31
Temporal Lobe	91	0.988071201	2.34E-58
Entorhinal Cortex	83	0.987938902	2.28E-53
Hippocampus	55	0.987649966	6.11E-36
Occipital Lobe	42	0.987097575	8.58E-28
Parietal Lobe	17	0.987046559	3.55E-12
Visual Cortex	34	0.985749141	1.07E-22
Putamen	16	0.983068148	2.21E-11
Hypothalamus	15	0.955939271	9.65E-10
Motor Neurons	12	0.951369771	6.13E-08
Myometrium	105	0.93770022	2.90E-54
Cerebrum	344	0.929249691	7.42E-166
Spinal Cord	19	0.911540172	5.24E-10
Induced Pluripotent Stem Cells	35	0.909845498	4.70E-17
Mesencephalon	41	0.891279245	4.22E-18
Ganglia	11	0.888268509	8.20E-06
Pluripotent Stem Cells	47	0.887997905	3.36E-20
Substantia Nigra	22	0.881612813	5.72E-10
Thalamus	16	0.88118802	1.29E-07
Prostate	352	0.844525608	5.56E-110
Blood Platelets	30	0.830525621	3.66E-10
Embryonic Stem Cells	83	0.827119532	6.34E-25
Plasma Cells	619	0.814779589	2.20E-159
Plasma	622	0.814599407	5.94E-160
Brain	1274	0.813036723	1.44E-316
Central Nervous System	1302	0.811873944	7.55E-321
Nervous System	1358	0.806921736	1.50E-323
Neural Stem Cells	11	0.755146073	0.003379265
Intestinal Mucosa	40	0.74643927	6.82E-08
B-Lymphocytes	851	0.742248614	2.44E-129
Muscle, Smooth	248	0.73160935	2.39E-36
Neurons	37	0.72880883	1.45E-06
Cell Line, Transformed	102	0.698633361	3.95E-12
HEK293 Cells	100	0.693945401	1.96E-11
Quadriceps Muscle	82	0.687370563	4.34E-09
Palatine Tonsil	72	0.682192254	8.81E-08
Parotid Gland	19	0.680947785	0.006303353
Embryoid Bodies	11	0.665376504	0.057461524
Heart Ventricles	124	0.665033427	2.09E-10
Nasopharynx	30	0.664841208	0.00176986
Retina	27	0.663968112	0.003174202
Subthalamic Nucleus	12	0.663374761	0.049972663
Testis	37	0.661115488	6.91E-04
Dendritic Cells	277	0.657506742	1.49E-19
Muscle, Skeletal	162	0.652023131	2.27E-11

Muscle, Striated	162	0.652023131	2.27E-11
Fetal Blood	151	0.641948835	1.64E-09
Clone Cells	115	0.641549286	1.52E-07
Blastocyst	14	0.640333192	0.068965016
Trophoblasts	11	0.617344063	0.177638503
Stem Cells	499	0.614746011	1.16E-18
HCT116 Cells	96	0.610921274	1.70E-04
Salivary Glands	24	0.605648834	0.073072337
Chorion	15	0.595994155	0.19786542
Lymphocytes	1737	0.59556586	2.33E-41
Heart	217	0.591729095	3.05E-06
Serum	104	0.585705556	0.002498331
Muscles	723	0.585616637	2.87E-15
Myocytes, Smooth Muscle	141	0.581154754	8.62E-04
Atrial Appendage	10	0.575676831	0.407157713
Sputum	151	0.574987439	0.001444128
Monocytes	506	0.57411284	9.72E-09
Muscle Cells	146	0.569282601	0.003799387
Fetus	337	0.565420867	3.45E-05
Heart Atria	13	0.561788882	0.440336888
Embryonic Structures	504	0.560923978	2.53E-06
Bone Marrow Cells	809	0.560418117	3.91E-09
Rectum	70	0.558437317	0.090625722
Mesenchymal Stem Cells	145	0.554601925	0.023007831
Myeloid Cells	997	0.550949995	3.84E-08
Osteoblasts	26	0.549172893	0.385220902
Germ Cells	33	0.543624727	0.385530633
Endothelial Cells	196	0.541871515	0.042824247
Chondrocytes	19	0.54101712	0.535763067
Tongue	105	0.540425793	0.151853146
Neutrophils	216	0.539414246	0.04540447
Urinary Bladder	70	0.531670484	0.359087921
Oocytes	15	0.528342065	0.703812377
Epithelial Cells	1933	0.527858559	3.60E-05
Precursor Cells, B-Lymphoid	14	0.5228282	0.767304891
Neck	138	0.522455043	0.361677334
U937 Cells	57	0.521980292	0.565658787
Granulocyte Precursor Cells	30	0.516456757	0.754920631
Macrophages	342	0.514554047	0.353291131
Hela Cells	201	0.513820785	0.498350179
Stromal Cells	54	0.509028106	0.818335116
Hematopoietic Stem Cells	106	0.508989577	0.748795899
Cell Line, Tumor	674	0.506541786	0.559732952
Intestines	1024	0.504651274	0.610957291
Lymphoid Tissue	818	0.50089711	0.929763011
Uterus	554	0.50014451	0.990523518
Stomach	55	0.499326671	0.986253872
Hep G2 Cells	102	0.499317074	0.981066877
Umbilical Cord	180	0.498852853	0.957658355
Mammary Glands, Human	12	0.498006593	0.980972223

Keratinocytes	48	0.495718964	0.918266499
Colon	783	0.494594325	0.604270631
Lymph	683	0.493676521	0.570714791
Lymph Nodes	671	0.493347842	0.554309438
Esophagus	13	0.489446567	0.895202927
K562 Cells	37	0.487982767	0.800257417
Colon, Sigmoid	27	0.485363438	0.79231478
Ileum	59	0.482764189	0.64681375
Retinal Pigment Epithelium	12	0.482758697	0.836161227
Retinal Pigment Epithelium	12	0.482758697	0.836161227
Intestine, Small	112	0.478286691	0.426758549
Penis	81	0.478107626	0.495421332
Jurkat Cells	21	0.471049972	0.645967256
Veins	133	0.468682902	0.211741648
Keloid	10	0.467717882	0.723675042
Umbilical Veins	113	0.467355013	0.230061433
Fibroblasts	392	0.466038538	0.02051735
Blood Vessels	171	0.465985619	0.124250774
Hepatocytes	188	0.461964636	0.071566741
Macrophages, Alveolar	117	0.459807068	0.132696243
Head	297	0.451237213	0.00373945
Islets of Langerhans	60	0.449360398	0.174581366
Pelvis	10	0.448440548	0.57228237
Placenta	114	0.442917219	0.035036705
Cicatrix	19	0.43734242	0.344238315
Mucous Membrane	480	0.435934018	1.36E-06
Membranes	521	0.433740624	1.97E-07
Foreskin	69	0.432293958	0.05161446
Caco-2 Cells	44	0.429161408	0.103796721
Cecum	15	0.429120781	0.341772137
Cecum	15	0.429120781	0.341772137
T-Lymphocytes	517	0.428162759	1.93E-08
T-Lymphocytes	517	0.428162759	1.93E-08
Organelles	12	0.416668894	0.317426915
Arteries	25	0.412855997	0.131345599
Cartilage	13	0.411797723	0.27072761
Cartilage	13	0.411797723	0.27072761
Adrenal Glands	129	0.408999007	3.52E-04
T-Lymphocytes, Regulatory	33	0.408956387	0.070161562
Thyroid Gland	85	0.406823416	0.00295572
HT29 Cells	17	0.403948299	0.170206701
Endometrium	264	0.403187555	5.66E-08
Liver	569	0.40165048	7.43E-16
Astrocytes	12	0.401316317	0.236424345
Pancreas	165	0.399273449	7.76E-06
Killer Cells, Natural	84	0.391968661	6.13E-04
Synovial Fluid	12	0.386545058	0.173456057
Lung	766	0.384948668	9.83E-28
Extremities	335	0.384869329	3.71E-13
Adrenal Cortex	99	0.382097334	4.95E-05

Eye	157	0.368126377	1.12E-08
Cumulus Cells	38	0.363428732	0.003559136
Skin	545	0.358255314	5.48E-30
Vulva	34	0.357925595	0.004126335
Mouth Mucosa	94	0.350726441	5.54E-07
Epithelium	183	0.347717137	1.10E-12
Cervix Uteri	38	0.342041214	7.48E-04
Knee	26	0.335686212	0.00371648
Kidney	614	0.324273857	1.42E-50
Adipocytes	81	0.323803498	4.09E-08
Femur	15	0.323684023	0.018029582
Trachea	63	0.321606996	9.56E-07
Glucagon-Secreting Cells	39	0.31352237	5.54E-05
Joints	26	0.312024771	9.03E-04
Synovial Membrane	26	0.312024771	9.03E-04
Spleen	23	0.298374273	8.13E-04
Ovary	699	0.282734865	1.86E-86
Abdomen	103	0.280899455	1.46E-14
Peritoneum	89	0.264779503	1.63E-14
Nasal Mucosa	93	0.253633432	2.06E-16
Chromosomes	34	0.252563786	5.88E-07
Omentum	76	0.252341232	8.00E-14
Foot	34	0.245432064	2.76E-07
Conjunctiva	59	0.245064662	1.23E-11
Fallopian Tubes	273	0.24469523	5.36E-48
Abdominal Fat	69	0.238090749	5.14E-14
Subcutaneous Fat, Abdominal	69	0.238090749	5.14E-14
Hand	11	0.232251152	0.002100277
Adipose Tissue	165	0.22720962	9.49E-34
Telomere	30	0.216509346	7.61E-08
Subcutaneous Fat	120	0.214690943	3.19E-27
Aortic Valve	10	0.122035438	3.48E-05

**Table S9: Association results of the SNPs with sleep duration and mid-sleep/chronotype (mid-sleep on free days adjusted for the sleep deficit on work days)**

MarkerName	Allele1	Allele2	Sleep duration			Mid-sleep		
			Effect	StdErr	P-value	Effect	StdErr	P-value
<b>rs9900428</b>	A	G	0.0351	0.0247	0.1548	-0.0387	0.0242	0.1097
<b>rs9907432</b>	A	G	0.0348	0.0242	0.1505	-0.0411	0.0238	0.08359
<b>rs7211029</b>	T	C	0.033	0.0241	0.1709	-0.0416	0.0237	0.07891

**Discovery  
phase**  
**N=4,270**

**Inclusion Criteria**

- Sleep assessment using MCTQ
- Sleep assessment on free days
- No use of alarm clock
- No shift-work during last 3 months
- No use of medication affecting sleep

**Cohorts included**

EGP  
ERF  
KORA  
KORCULA  
MICROS  
NESDA  
ORCADES

**Replication  
phase**  
**N=30,377**

**Inclusion Criteria**

- Sleep assessment using any tool
- No use of sleep medication

**Cohorts included**

ARIC  
CHS  
CROATIA-SPLIT  
FHS  
EGCUT  
ERF-ext  
MrOS  
NTR  
RS  
SOF  
QIMR

Figure S2

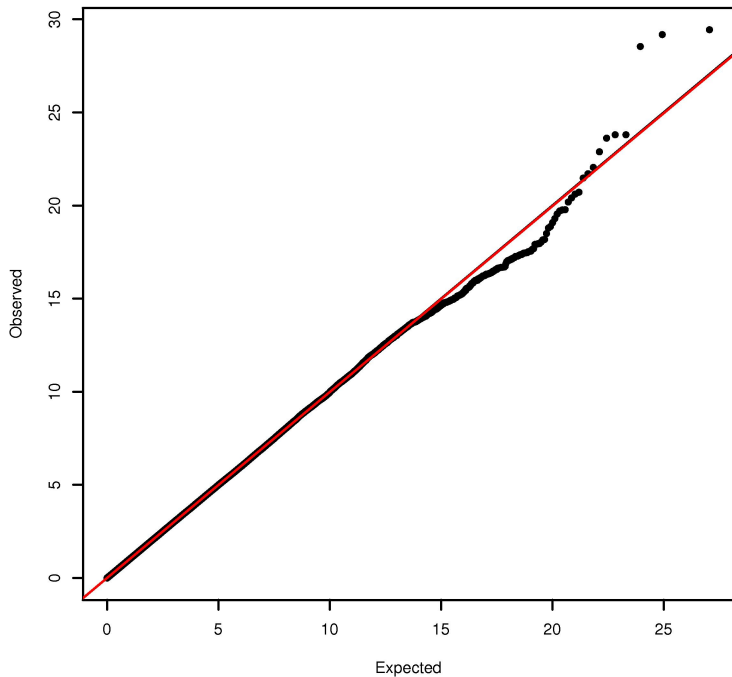


Figure S3

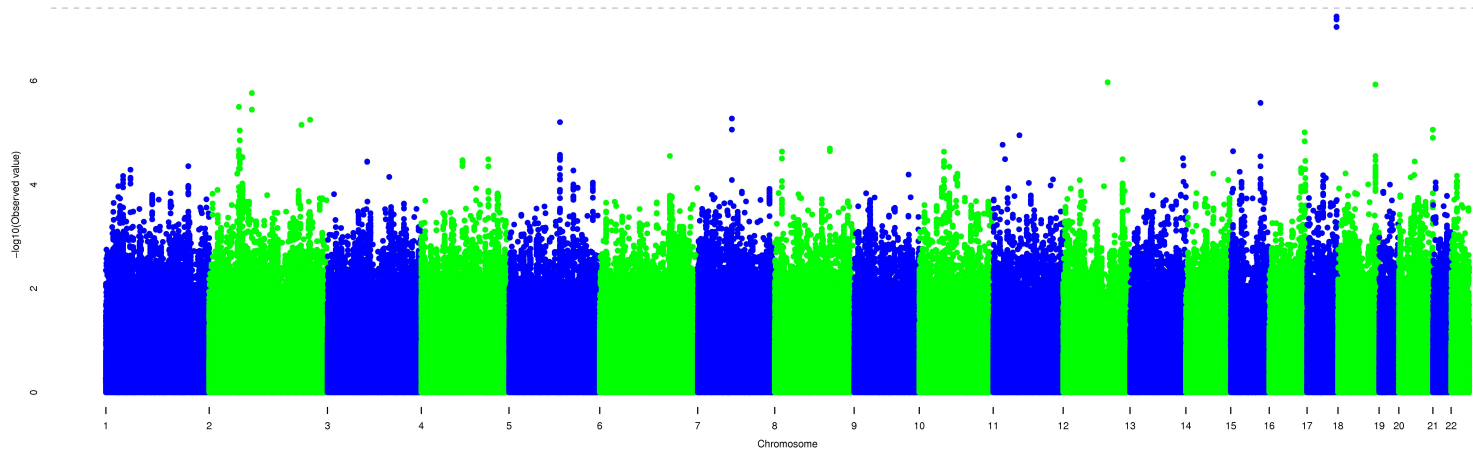


Figure S4

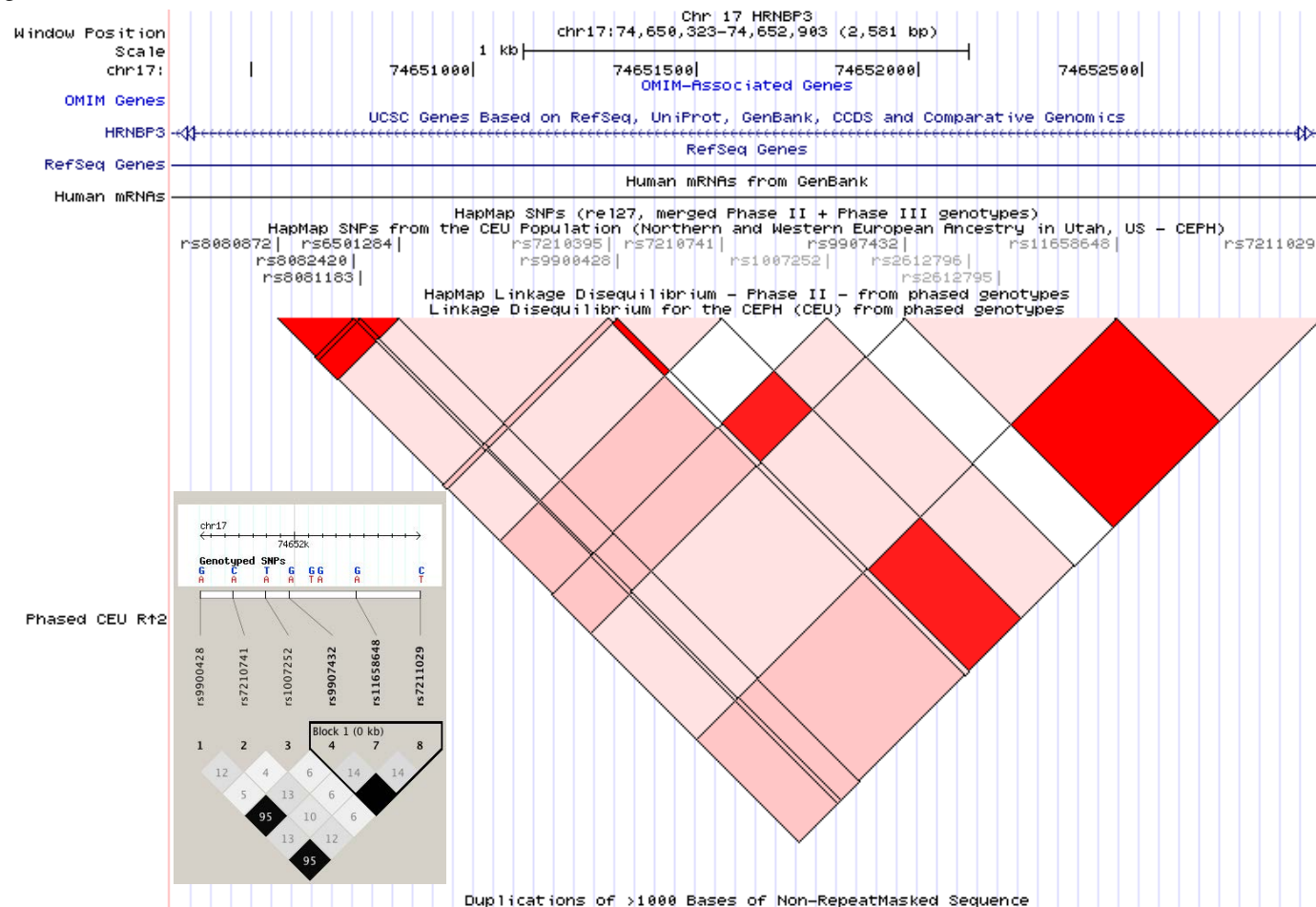


Figure S6

