Multi-ancestry genome-wide gene-sleep interactions identify novel loci for blood pressure

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Abstract

Long and short sleep duration are associated with elevated blood pressure (BP), possibly through effects on molecular pathways that influence neuroendocrine and vascular systems. To gain new insights into the genetic basis of sleep-related BP variation, we performed genome-wide gene by short or long sleep duration interaction analyses on four BP traits (systolic BP, diastolic BP, mean arterial pressure, and pulse pressure) across five ancestry groups using 1 degree of freedom (1df) interaction and 2df joint tests. Primary multi-ancestry analyses in 62,969 individuals in stage 1 identified 3 novel loci that were replicated in an additional 59,296 individuals in stage 2, including rs7955964 (*FIGNL2/ANKRD33*) showing significant 1df interactions with long sleep duration and rs73493041 (*SNORA26/C9orf170*) and rs10406644 (*KCTD15/LSM14A*) showing significant 1df interactions with short sleep duration ($P_{int} < 5 \times 10^{-8}$). Secondary ancestry-specific two-stage analyses and combined stage 1 and 2 analyses additionally identified 23 novel loci that need external replication, including 3 and 5 loci showing significant 1df interactions with long and short sleep duration, respectively. Multiple genes mapped to our 26 novel loci have known functions in sleep-wake regulation, nervous and cardiometabolic systems. We also identified new gene by long sleep interactions near five known BP loci (1Mb) including *NME7*, *FAM208A*, *MKLN1*, *CEP164*, and *RGL3/ELAVL3* ($P_{int} < 5 \times 10^{-8}$). This study indicates that sleep and primary mechanisms regulating BP may interact to elevate BP level, suggesting novel insights into sleep-related BP regulation.

Introduction

Hypertension (HTN), including elevations in systolic blood pressure (SBP) and/or diastolic blood pressure (DBP), is a major risk factor for cardiovascular diseases, stroke, renal failure and heart failure[1]. The heritability of HTN is estimated to be 30–60% in family studies[2, 3]. Recent well-powered large genome-wide association studies (GWAS) of blood pressure

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(BP) have identified over 1,000 loci; however, in total these explain less than 3.5% of BP variation[4–16]. Gene-environment (G×E) interaction analyses have been proposed to explain additional heritability and identified novel loci for traits associated with cardiometabolic diseases[17–19].

Long and short sleep durations are associated with elevated BP, possibly through effects on molecular pathways that influence neuroendocrine and vascular systems[20, 21]. Recent multi-ancestry interaction analyses between genetic variants and sleep duration (gene-sleep for short) on blood lipid traits have identified novel loci and potentially distinct mechanisms for short- and long-sleep associated dyslipidemia, and suggest a modification effect of sleep-wake exposures on lipid biology[19]. We hypothesize that differences in sleep duration may also modify the effect of genetic factors on BP. Assessment of genetic association studies accounting for potential gene-sleep interactions may help identify novel BP loci and reveal new biological mechanisms that can be explored for treatment or prevention of HTN.

Within the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Gene-Lifestyle Interactions Working Group[22], we investigate gene-sleep interactions on BP traits in 122,265 individuals from five ancestry groups. We utilize both the 1 degree of freedom (df) test of interaction effect and the 2df joint test of main and interaction effects[23], and identify novel loci for BP.

Materials and methods

We performed genome-wide meta-analysis of gene-sleep interactions on four BP traits (SBP, DBP, mean arterial pressure [MAP], and pulse pressure [PP]) in 30 cohorts of five ancestry groups in two stages (Supplementary Notes). Stage 1 discovery analyses included 62,969 individuals of European (EUR), African (AFR), Asian (ASN), Hispanic (HIS), and Brazilian (BRZ) ancestries from 16 studies (Supplementary Tables 1–3). Stage 2 replication analyses included 59,296 individuals of EUR, AFR, ASN and HIS ancestries from 14 additional studies (Supplementary Tables 4–6). We examined long total sleep time (LTST) and short total sleep time (STST) separately as lifestyle exposures. Given the heterogeneity of age, sleep duration and BP levels across cohorts and ancestry groups, as well as differences in how sleep duration was assessed (Supplementary Tables 2 and 5), we followed procedures used in prior research[19] to categorize 20% of each sample as long sleepers and 20% as short sleepers based on responses to questionnaires, accounting for age and sex variability within each cohort (Supplementary Methods).

The overall study design is described in Fig. 1. Gene-sleep interaction analyses were performed adjusting for age, sex, population structure, and other cohort-specific covariates in each ancestry of each cohort. Since BMI is associated with both sleep and BP[24, 25], we performed additional interaction analyses adjusted for BMI to identify genetic loci through biological pathways independent of obesity. Inverse-variance weighted meta-analysis for the 1 degree of freedom (df) interaction term (P_{int}), and 2 df joint fixed-effects meta-analysis of the combined main and interaction effects (P_{joint}) using Manning et al's method[23] were performed across multi-ancestry in stage 1 and stage 2 separately. Secondary ancestry-specific meta-analyses were performed restricted to EUR and AFR groups. We performed

extensive study-level and meta-level quality controls as described in Supplementary Methods.

Genetic variants with P_{int} or P_{joint} $<10^{-6}$ in stage 1 were followed up in stage 2 replication analyses and subsequently meta-analyzed with stage 1 summary statistics. The replication significance threshold was defined as stage 2 P<0.05 and stage 1 + 2 P<5×10^{-8}, with consistent directions of association effects. To maximize the statistical power, we also performed genome-wide combined stage 1 and 2 meta-analyses in multi-ancestry and EUR groups. Additional novel loci were reported at a stricter significant threshold (P<3.125×10^{-9}), accounting for 2 independent BP traits, 2 exposures, 2 tests (joint and interaction), with and without BMI adjustment. Novel loci replicated in two-stage analyses and additional loci identified in combined analyses were followed up for associations with relevant traits and bioinformatics analyses.

This work was approved by the Institutional Review Board of Washington University in St. Louis and complies with all relevant ethical regulations. For each of the participating cohorts, the appropriate ethics review board approved the data collection and all participants provided informed consent.

Results

Genome-wide gene-sleep interaction analyses

The Miami and QQ plots of stage 1 discovery analyses in multi-ancestry, EUR and AFR groups are provided in Supplementary Figs 1–6. 1,976 genetic variants with P_{int} or $P_{joint}<10^{-6}$ were followed up for replication analyses. Of these, 1,081 variants were available in stage 2 cohorts and passed quality control, of which 268 variants showed P_{joint} or P_{int} <0.05.

Our primary two-stage multi-ancestry analyses replicated 3 novel loci ($r^2<0.1$ and >1Mb from any previously identified BP locus) using the 1df interaction test. Among these loci, rs7955964 (*FIGNL2/ANKRD33*) showed significant 1df interactions with LTST, while rs73493041 (*SNORA26/C9orf170*) and rs10406644 (*KCTD15/LSM14A*) revealed significant 1df interactions with STST ($P_{int}<5×10^{-8}$; Table 1). The regional association plots are shown in Supplementary Fig. 7. Consistent directions of main and interaction effects were observed across different cohorts (Fig. 2). Note that since rs7955964 and rs10406644 are common only in AFR and HIS cohorts (minor allele frequency [MAF] > 1%), the association effects may be driven by African ancestral alleles. With and without adjustment for BMI showed similar association results at those three loci (Table 1). Using 2df joint test we identified 9 loci that were within 1Mb from previously reported BP loci ($P_{joint}<5×10^{-8}$; Supplementary Table 7). However, none of these loci showed nominal significant 1df interaction association with LTST or STST ($P_{int}>0.05$).

In secondary ancestry-specific two-stage analyses restricted to EUR or AFR individuals, the 1df interaction test did not identify any significant locus. The 2df joint test in EUR group identified 1 locus near previously reported BP loci (1Mb; Supplementary Table 7). The 2df joint test in AFR group identified 3 novel loci after incorporating

interactions with LTST (stage 1 P_{joint} <5×10^{-8} and stage 2 P_{joint}<0.05, with consistent directions of main effects), including rs111887471 (*TRPC3/KIAA1109*), rs114043188 (*ANK*), and rs138967672 (*RP11–322L20.1/RP11–736P16.1*) (Supplementary Table 8 and Supplementary Fig. 8). However, these 3 variants did not survive our formal replication criteria of stage 1+2 P<5×10^{-8}, possibly reflecting heterogeneity between discovery and replication cohorts.

Genome-wide combined stage 1 and stage 2 meta-analyses (Miami and QQ plots in Supplementary Figs 9–12) additionally identified 20 loci near previously reported BP loci (1Mb) and 56 unreported loci (>1Mb from previously reported BP) with P_{joint} or P_{int}<5×10^{-8} (Supplementary Tables 9–11). Loci near known BP genes, including *NME7, FAM208A, MKLN1, CEP164*, and *RGL3/ELAVL3*[7–11] showed significant 1df interactions with LTST (P_{int}<5×10^{-8}; Supplementary Table 9). Among the 56 unreported loci, 20 loci passed a stricter significance threshold accounting for multiple comparisons (P_{joint} or P_{int} <3.125×10^{-9}; Supplementary Table 10 and Supplementary Fig 13). Among these 20 novel loci, 3 loci showed significant 1df interaction with LTST and 5 loci showed genome-wide significant 1df interactions with STST (P_{int}<5×10^{-8}; Supplementary Table 10). Replication in independent datasets is needed to validate those unreported loci. We also looked up the previously validated 362 BP loci[4–15] and 113 sleep duration loci[26] in the combined analyses, but none of these showed significant 1df interactions after accounting for multiple comparisons (P_{int}>10^{-4}; Supplementary Tables 12–15).

We estimated the variance of BP traits explained by 3 replicated and 23 additional novel loci (3 in AFR two-stage analyses and 20 in combined analyses) using the R package VarExp[27] (Supplementary Table 16). The 3 replicated novel variants together explained 0.002–0.039% and 0.304–0.939% of BP variation in EUR and AFR, respectively. The other 23 variants additionally explained 0.230–0.419% and 0.806–2.597% of BP variation in EUR and AFR. Given the limited sample sizes in the AFR group, the estimation of BP variation in AFR is likely inflated.

Associations with other relevant traits

We looked up the associations between the 3 replicated and 23 additional novel loci with cardiovascular diseases, stroke, chronic kidney disease, and self-reported and objective (derived from 7-day accelerometry) sleep traits using publicly available genome-wide summary statistics from large GWAS[26, 28–37] (Supplementary Tables 17–22). One of the replicated loci rs73493041 (*SNORA26/C9orf170*) was associated with self-reported chronotype (morningness vs eveningness) (P=9.1×10^{-6}; Supplementary Table 21). Among the other novel loci, rs17036094 (*PSRC1/MYBPHL*) was associated with coronary artery disease and myocardial infarction (P 0.005; Supplementary Table 18), and rs140526840 (*FSTL5*) was associated with chronic kidney disease (P=0.006; Supplementary Table 20),

Bioinformatics analyses

All of the 26 novel variants were mapped to intergenic or intronic regions using HaploReg[38], including 4 in promoter histone marks, 11 in enhancer histone marks, 10 in DNAse, 3

altered the binding sites of regulatory proteins and 2 conserved elements (Supplementary Table 23).

Among the 3 replicated novel loci, rs73493041 (*SNORA26/C9orf170*) was an eQTL for *GAS1* in suprapubic skin using GTEx (v8)[39] (Supplementary Table 24). Using PLINK pruning and SNPsea[40], rs7955964 (*SNORA26/C9orf170*) was mapped to a region of 10 genes (Supplementary Table 25), including *ANKRD33* and *NR4A1,* implicated in sleep-wake control regulation and the neurovascular system[41, 42]. Rs10406644 (*KCTD15/ LSM14A*) was mapped to a region overlapping with 9 genes (Supplementary Table 26), including *KCTD15* and *CHST8,* previously associated with adiposity traits and involved in neurodevelopmental and neuropsychiatric diseases[43–45] (see Discussion).

Among the other 23 novel loci, 4 variants showed strong eQTL evidence across various tissues such as blood and adipose tissue (Supplementary Table 24). 14 loci were mapped to genes with known functions in cardiac and nervous systems (e.g., *TRPC3*[46], *RYR2*[47], *ANK2*[48]*, GJA4*[49] and *SORT1*[50]) and associated with other cardiometabolic (e.g., *HTR1A*[51], *PSRC1*[52], *PSKH1*[53]), inflammatory (e.g., *IL33*[54]), cognition (e.g., *FRMD4A*[55]) and psychiatric traits (e.g., *NFATC3*[56]) (Supplementary Tables 25 and 26).

In total, 11 novel loci harbored genes implicated in Mendelian syndromes such as ventricular tachycardia and cryptogenic cirrhosis. 13 loci harbored one or more genes with potential drug targets (Supplementary Tables 25 and 26).

We performed tissue and pathway enrichment analyses using annotated genes under novel association regions using FUMA[57] (Supplementary Tables 27 and 28). Genes under the association regions in gene-LTST interaction analyses were enriched in multiple artery and cardiac muscle related pathways (Supplementary Table 29).

Discussion

We performed gene-sleep interaction analyses on BP using 122,265 individuals from 5 ancestry groups in 30 studies, using both a 1df test of interaction effect and a 2df joint test of main and interaction effects. Following a two-stage design, we identified 3 novel loci that were replicated in additional samples, including rs7955964 (*FIGNL2/ANKRD33*) showing significant interactions with LTST, and rs73493041 (*SNORA26/C9orf170*) and rs10406644 (*KCTD15/LSM14A*) showing significant interactions with STST ($P_{int}<5\times10^{-8}$). Secondary analyses additionally identified 3 novel loci with weak replication evidence in AFR groups using 2df joint test. Combined stage 1 and 2 analyses identified another 20 novel loci after accounting for multiple comparisons (P_{joint} or $P_{int}<3.125\times10^{-9}$), which require external replication. The associations were largely unchanged after additionally adjusting for BMI. Collectively, these 26 loci explained 0.23–0.43% of BP variation in EUR and 1.33–2.96% BP variation in AFR groups.

The emergence of novel loci after considering gene-sleep interactions suggests an important modifying role of sleep on BP regulation, which involves both central and peripheral regulation (including the brain, adrenal glands, kidneys, and vasculature). Insufficient or short sleep can increase BP through effects on elevating sympathetic nervous system activity

and altering hypothalamic-pituitary-adrenal (HPA) axis activities, leading to hormonal changes, endothelial dysfunction, insulin resistance, and systemic inflammation[20, 58]. The mechanisms underlying the association between long sleep duration and BP are less well understood, and may reflect circadian misalignment in a 24-hour period, including disrupted sleep-wake cycle, a misalignment of internal biological clocks with the external environment, and desynchronized central and peripheral clocks in tissues relevant for BP control[59]. The importance of circadian control of BP is evident by the normal nocturnal decline ("dipping") in BP. Non-dipping of BP, associated with increased mortality, is observed with both sleep disturbances and abnormalities of sodium transport in the kidney[60, 61]. Our data suggest that sleep and renal and neuro-endocrine control of BP may interact to influence susceptibility to HTN. The novel loci found by gene-LTST and gene-STST interaction analyses were distinct, supporting the different mechanisms of short and long sleep modifying BP. Similarly, in prior gene-sleep interaction analyses for blood lipids, LTST and STST each also modified gene effects in a non-overlapping pattern[19].

Primary two-stage multi-ancestry analyses identified 3 novel loci. At rs7955964 (*FIGNL2/ANKRD33*), *ANKRD33* is expressed in retinal photoreceptors and the pineal gland and acts as a transcriptional repressor for CRX-activated photoreceptor gene regulation[41]. Given the importance of light in the central regulation of circadian rhythms, long sleep- a circadian disruptor- may interact with this gene to influence BP[60]. Additionally, *NR4A1* (also at rs7955964) is a member of the nuclear hormone receptors, which regulate neurohormonal systems including dopamine and norepinephrine and cardiac stress responses[42]. At rs10406644 (*KCTD15/LSM14A*), *CHST8* and *KCTD15* are associated with adiposity traits[43, 44] and *GPI* functions in glucose metabolism and immune system pathways[62, 63]. Short sleep may exacerbate weight gain and metabolic dysfunction[64], thus amplifying effects of this locus on BP. *KCTD15* belongs to a gene family involved in neurodevelopmental and neuropsychiatric diseases[45]. Rs73493041 (*SNORA26/C9orf170*) was an eQTL for *GAS1*, a pleiotropic regulator of cellular homeostasis and widely expressed in the central nervous system[65, 66]. This variant was also significantly associated with self-reported chronotype, an indicator of circadian preference (P=9.1×10^{-6}; Supplementary Table 20).

Given the high prevalence of HTN in African Americans, there is a critical need to identify modifiable risk factors. Notably, African Americans have poorly controlled HTN as well as circadian abnormalities in BP regulation[67]. They also have a higher prevalence of short and long sleep duration compared to individuals of European ancestry[68, 69], likely due to combinations of social-environmental exposures and genetic and epigenetic susceptibility[70]. In AFR specific gene-LTST analyses we identified 3 unreported loci, including two loci mapped to *TRPC3* and *ANK2* with known functions in cardiac ion (Na^+ and Ca^{2+}) homeostasis[46, 48]. These associations in AFR may reflect differences in BP control with individuals of African ancestry having greater sodium sensitivity[71], with BP effects amplified by disrupted circadian rhythm regulation due to long sleep[61]. While intriguing, these associations were observed in African Americans ($P_{joint} < 5 \times 10^{-8}$) and the only available replication sample was individuals of African ancestry from the UK ($P_{joint} < 0.05$). There may be a systematic difference of the admixture structure between the discovery and replication cohorts. Future analyses using larger AFR samples will be

needed to validate these findings and further identify the potential for sleep disturbances to interact with BP regulatory systems in AFR who are at increased risk for HTN-associated morbidities.

Although we did not observe significant 1df interactions with sleep duration on the 362 previously reported BP or 101 sleep duration variants (Supplementary Tables 12–15), we identified 30 loci within 1Mb from previously reported BP regions (Supplementary Tables 7 and 9). Among those, variants in/near *NME7*, *FAM208A*, *MKLN1*, *CEP164*, and *RGL3/ELAVL3* showed significant 1df interactions with LTST ($P_{int}<5\times10^{-8}$; Supplementary Table 9). Some of these genes have known functions in neuronal systems, including *MKLN1* regulating the internalization and transport of the $GABA_A$ receptor[72, 73] and *ELAVL3* encoding a neural-specific RNA-binding protein involved in neuronal differentiation and maintenance[74].

In this study we defined short and long sleep duration using self-reported questionnaires, which can result in misclassification[75], potentially reducing statistical power. Although we used a within cohort approach for harmonizing sleep duration that accounted for age and sex differences across cohorts, there may be systematic residual differences in sleep assessments that resulted in heterogeneity across our samples. Future work using objective measurements (e.g., polysomnography and actigraphy data) may provide further insight into sleep-related BP mechanisms.

Some of our most interesting findings - and ones with high potential public health impact due to the burden of extreme sleep duration and HTN in AFR group. Unfortunately, limited samples of AFR were available for replication. We identified 1,976 variants with significant association effect in gene-sleep interaction analyses in stage 1. However, only 1,081 of those variants were available in stage 2 analyses. Most of the unavailable variants in stage 2 had been identified in non-EUR cohorts and were rare in EUR populations (MAF<1%). Future studies following-up these "missing" variants in diverse groups and additional studies of minority populations are needed to further understand mechanisms for BP regulation that are modulated by sleep. In addition, some of our findings were mapped to large genomic regions covering many genes. Further fine-mapping analyses using sequencing data or biochemistry experiments may further clarify the causal variants.

In summary, we performed a large-scale gene-sleep interaction meta-analyses in multi-ancestry groups. In addition to identifying interactions at a genome-wide significant level near 5 previously reported BP regions, we identified 3 novel loci with formal replication and 23 novel loci that need external replication. Multiple genes showing significant interactions with long or short sleep duration were functional in tissues relevant for BP control, and associated with circadian, metabolic, and neuropsychiatric traits. Prior research indicates that extreme sleep durations (short or long) are strongly associated with cardiovascular disease and mortality through causal and noncausal pathways[20, 21]. Our data suggest that interactions between sleep and BP-regulating genes may contribute to the increased cardiovascular morbidity observed with extreme sleep duration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acknowledgments

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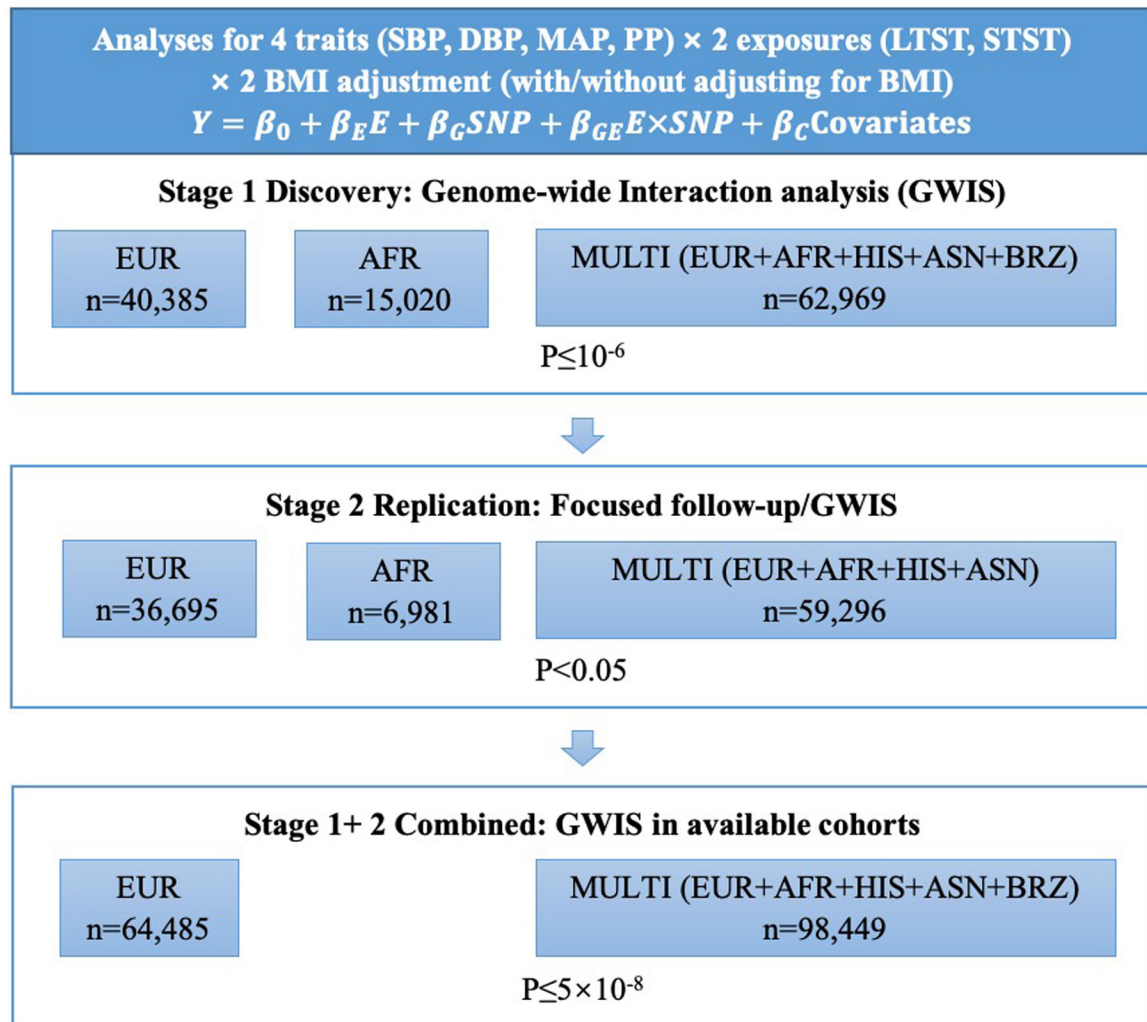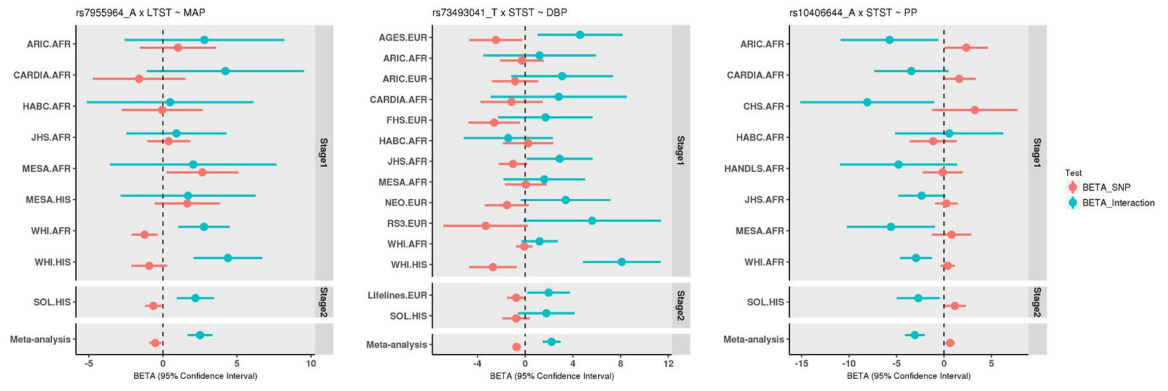
Fig. 1.
Study overview.

Fig. 2.
Forest plots of 3 replicated novel loci identified in genome-wide gene- sleep 1df interaction analyses in multi-ancestry population.

Table 1.

Replicated novel BP loci identified incorporating gene-sleep interactions with and without BMI adjustment.

Exposure	rsID	Gene(s)	Chr: position (Build 37)	Alleles (E/A)	EAF	Trait	Stage	BMI adjustment	N	β_{SNP}	SE_{SNP}	β_{Int}	SE_{Int}	P_{Joint}	P_{Int}
LTST	rs7955964	FIGNL2, ANKRD33	12:52281279	A/T	0.896	MAP	1	Without BMI	18583	−0.400	0.290	2.711	0.582	1.75×10^{-5}	1.34×10^{-6}
								with BMI	18583	−0.462	0.279	2.768	0.546	2.48×10^{-6}	2.10×10^{-7}
							2	Without BMI	12335	−0.621	0.289	2.163	0.632	2.52×10^{-3}	5.49×10^{-4}
								with BMI	12327	−0.519	0.281	2.210	0.613	1.72×10^{-3}	2.66×10^{-4}
							1+2	Without BMI	29985	−0.517	0.208	2.505	0.433	1.11×10^{-7}	**4.40×10^{-9}**
								with BMI	29957	−0.500	0.201	2.577	0.413	**6.74×10^{-9}**	**2.94×10^{-10}**
STST	rs73493041	SNORA26, C9orf170	9:89849304	T/C	0.959	DBP	1	Without BMI	36858	−0.725	0.229	2.336	0.471	4.65×10^{-6}	3.6×10^{-7}
								with BMI	36858	−0.723	0.219	2.235	0.456	5.16×10^{-6}	5.18×10^{-7}
							2	Without BMI	24413	−0.763	0.321	1.888	0.705	5.44×10^{-3}	9.43×10^{-3}
								with BMI	24385	−0.704	0.335	1.875	0.704	1.09×10^{-2}	1.27×10^{-2}
							1+2	Without BMI	61271	−0.724	0.185	2.213	0.387	**3.62×10^{-8}**	**1.30×10^{-8}**
								with BMI	61243	−0.709	0.182	2.132	0.381	7.15×10^{-8}	**2.58×10^{-8}**
	rs10406644	KCTD15, LSM14A	19:34595645	A/G	0.095	PP	1	Without BMI	15021	0.542	0.275	−3.194	0.605	1.26×10^{-6}	1.35×10^{-7}
								with BMI	12921	0.565	0.306	−3.382	0.677	5.23×10^{-6}	4.81×10^{-7}
							2	Without BMI	11401	1.142	0.587	−2.702	1.163	4.59×10^{-2}	2.02×10^{-2}
								with BMI	11373	1.102	0.582	−2.533	1.155	6.08×10^{-2}	2.83×10^{-2}
							1+2	Without BMI	26422	0.648	0.249	−3.067	0.536	1.39×10^{-7}	**7.59×10^{-9}**
								with BMI	24294	0.678	0.271	−3.135	0.584	8.56×10^{-7}	**4.35×10^{-8}**