Original Article

International Genome-Wide Association Study Consortium Identifies Novel Loci Associated With Blood Pressure in Children and Adolescents

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Background—Our aim was to identify genetic variants associated with blood pressure (BP) in childhood and adolescence.

Methods and Results—Genome-wide association study data from participating European ancestry cohorts of the Early Genetics and Lifecourse Epidemiology (EAGLE) Consortium was meta-analyzed across 3 epochs; prepuberty (4–7 years), puberty (8–12 years), and postpuberty (13–20 years). Two novel loci were identified as having genome-wide associations with systolic BP across specific age epochs: rs1563894 (*ITGA11*, located in active H3K27Ac mark and transcription factor chromatin immunoprecipitation and 5′-C-phosphate-G-3′ methylation site) during prepuberty (P=2.86×10^{-8}) and rs872256 during puberty (P=8.67×10^{-9}). Several single-nucleotide polymorphism clusters were also associated with childhood BP at P<5×10^{-3}. Using a P value threshold of <5×10^{-3}, we found some overlap in variants across the different age epochs within our study and between several single-nucleotide polymorphisms in any of the 3 epochs and adult BP-related single-nucleotide polymorphisms.

Conclusions—Our results suggest that genetic determinants of BP act from childhood, develop over the lifecourse, and show some evidence of age-specific effects. **(*Circ Cardiovasc Genet*. 2016;9:266-278. DOI: 10.1161/CIRCGENETICS.115.001190.)**

Key Words: blood pressure ■ children ■ genetic epidemiology ■ Genome-Wide Association Study ■ hypertension ■ prehypertension

Systolic and diastolic blood pressure (SBP and DBP) are complex phenotypes, with known environmental and genetic risk factors.[1] Elevated SBP and DBP are associated with premature mortality[2,3] and cardiovascular diseases.[2,4–9]

Clinical Perspective on p 278

Recent genome-wide association studies (GWAS) have identified genetic variants associated with adult SBP and DBP and hypertension.[10–24] Several of these loci are in biologically plausible candidate genes, for example, those that influence the renin–angiotensin system.[25] There are established patterns of age-related changes in BP in industrialized populations, which support a potential interaction of genetic variants with age-related changes to environmental exposures in these populations.[26,27] For genetic variants that directly modulate childhood BP, effects might change with age, might differ between developmental periods (early life, childhood, and adolescence), and might also differ to those variants that act in adulthood.

Children and adolescents are rarely treated with antihypertensives, whereas from middle age onwards, an increasing proportion of adults are using such medications.[26] Consequently, it is easier to examine genetic variants that are associated with untreated SBP and DBP in children. Variation in SBP, and to

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a lesser extent DBP, in adolescence and early adulthood is associated with subsequent adult risk of coronary heart disease and stroke.[28,29] Understanding the risk factors, including genetic variation, that are associated with SBP and DBP through childhood and into adolescence may therefore inform an improved understanding of the life course pathogenesis of adult hypertension and cardiovascular disease. GWAS of BP in children to date have been limited to investigations of cross-sectional BP in individual cohorts,[30] often in non-European populations.[31,32]

The principal aim of the current study was to identify age-specific genetic associations with SBP and DBP across childhood and adolescence. The secondary aim was to compare results from this GWAS to published results from adult GWAS of BP.

Methods

EAGLE Consortium: BP Working Group

Seven pregnancy/birth or childhood cohorts of European ancestry from the Early Genetics and Lifecourse Epidemiology (EAGLE) Consortium BP working group with completed genome-wide genotyping and measures of SBP and DBP on participants between the ages of 4 and 20 years contributed to this study.

Each study was conducted with appropriate institutional ethics approval, and written informed consent was obtained from participants or their main caregivers. Each study conducted their own GWAS analyses, and results were then pooled using meta-analysis. The methodology for recruitment of participants and measurement of BP for each cohort are described in the Data Supplement.

Only those participants who had at least one BP measurement at, or before, 20 years of age were included in analyses. With the exception of the Brisbane Longitudinal Twin Study (BLTS), all analyses were restricted to children from singleton pregnancies, the first born (with relevant genotype and phenotype data) from cohorts that included siblings, or a randomly selected child from those that included twins. BLTS, which included all twins and siblings, took into account both zygosity and relatedness using the statistical package Merlin[33] during their GWAS.

ICBP

We used GWAS data from studies contributing to the International Consortium of Blood Pressure (ICBP) on adults who were recruited for classical or genetic epidemiological purposes from general population samples[17] to compare with associations identified in EAGLE.

Genotyping and Imputation

Single nucleotide polymorphisms (SNPs) were genotyped on one of the following platforms: Affymetrix, Illumina, or Perlegen. Predefined marker filters were applied before imputation (Hardy–Weinberg equilibrium $>10^{-6}$, MAF >0.01, SNP call rate >95%). Each study imputed SNPs by combining their study's genotyped SNPs with HapMap Phase II CEU SNPs samples, preferably using release 22 of HapMap, build 36. Imputation results are summarized as an allele dosage defined as the expected number of copies of the minor allele at that SNP (a fractional value between 0.0 and 2.0) for each genotype. Further details are provided in Data Supplement and Table 1.

Statistical Analysis

Cross-Sectional GWAS

Cross-sectional associations were performed for SBP and DBP in 3 age epochs over childhood/adolescence. These epochs were chosen before any analyses and were based on previous evidence of the ages in European populations that girls go through mencarche, boy's voices break, and both sexes have a growth spurt and in part pragmatically, relating to available data in the participating studies. These epochs were the following: prepuberty (4 to ≤7 years), puberty (8 to ≤12 years), and postpuberty (13 to ≤20 years; Table 1 and Figure I in the Data Supplement).

Genetic analyses assumed an additive model for SNP-based main effects. All analyses were adjusted for age, height, and weight, consistent with analyses used in GWAS of BP in adults (adjusted for body mass index).[14,18,20,24,34] The Z-score was calculated per individual as the difference between an individual's BP measure and the average BP measure for that given age epoch and sex for each cohort. This was then divided by the standard deviation of the BP measure across the particular cohorts' age, epoch, and sex. Those Z-scores were then regressed against each SNP (additive) adjusting for age, sex, and height of the individual. Participants could contribute to >1 epoch but only one measurement time point contributed to each epoch. The median measurement time was selected in the event that a cohort had repeatedly measured data within a single epoch.

Meta-Analyses

Separate genome-wide meta-analyses were run for SBP and DBP for each epoch using the inverse-variance weighting method in Meta-Analysis (software for GWAS) (www.sph.umich.edu/csg/abecasis/metal).[38] Before meta-analysis, rare variants were excluded (MAF>0.01; Table I in the Data Supplement). Double genomic control correction was applied (once during the study-specific analyses [before the meta-analysis] and repeated on the statistics resulting from the meta-analysis). Heterogeneity between results from individual studies was assessed using I^2 and a Q-statistic. Further filtering based on N-effectives >70% was also used. QQ-plots for the meta-analysis of each BP outcome across each epoch and data set are presented in Figure II in the Data Supplement. A threshold of $P \leq 5\times10^{-8}$ was used to define genome-wide levels of significance. An association of an SNP cluster was defined as ≥2 nearby variants each reaching a threshold of $P \leq 5\times10^{-3}$. This more liberal statistical significance level ($P \leq 5\times10^{-3}$) was used to ensure the inclusion of variants that could potentially have been identified in larger samples of children.

Exploring Functionality

We used the Encyclopedia of DNA Elements[35] to investigate the functionality (transcriptional active region, H3K27Ac active regulatory

Table 1. List of Participating Cohorts With GWAS and SBP and DBP Data Available in Children

Cohort	Time Frames, epochs		
	Prepubertal, (4–7 y)	Pubertal, (8–12 y)	Postpubertal, (13–20 y)
Raine	1276	1251	1009
GenerationR	1847		
ALSPAC	5967	5750	4050
Lisa Plus		282	
YFS	400	842	
INMA	600		
BLTS		298	117
Total	10 090	8423	5176

Number of subjects per cohort per time frame used in analyses. ALSPAC indicates The Avon Longitudinal Study of Parents and Children Bristol, UK; BLTS, Brisbane Longitudinal Twin Study, Brisbane, Queensland, Australia; GenerationR, The Generation R Study Group, Rotterdam, The Netherlands; INMA, Spanish INMA—Infancia y Medio Ambiente, Barcelona, Catalonia, Spain; Lisa Plus, Influence of lifestyle factors on the development of the immune system and allergies in East and West Germany Plus the influence of traffic emissions and genetics, Neuherberg, Germany; Raine, The Western Australian Pregnancy (Raine) Cohort, Perth, Western Australia; YFS; The Cardiovascular Risk in Young Finns Study, Turku, Finland.

elements, DNase hypersensitivity transcription factor–binding site information from chromatin immunoprecipitation (ChIP) analysis, and 5′-C-phosphate-G-3′ (CpG) methylation levels) of identified BP-related SNPs.

Comparing Findings Across Epochs and in Adults

Any variants identified as associated with SBP or DBP at $P \leq 5\times10^{-3}$ in any age epoch was examined in (1) the other 2 epochs in our study; (2) in adult participants from the ICBP, and (3) in SNPs identified as associated with adult CHD using the results from Coronary Artery Disease Genome-Wide Replication and Meta-Analysis (CARDIoGRAMplusC4D),[36] a consortium designed to identify novel susceptibility loci for coronary artery disease and myocardial infarction.[37]

We also examined whether variants associated with adult BP in ICBP at $P \leq 5 \times 10^{-3}$ for association with BP in any of the 3 epochs in our study.

Meta-analyses were conducted in Meta-Analysis (software for GWAS). The statistical software package R version 2.12.1[39] was used to produce all Manhattan Plots. Regional association plots were produced using LocusZoom.[40]

Results

Seven cohorts contributed to meta-analyses, a total of 10 090 individuals for the prepubertal epoch, 8423 individuals for the pubertal epoch, and 5176 individuals for the postpubertal epoch (Table 1). Manhattan plots for SBP and DBP by epoch are presented in Figure III in the Data Supplement. Regional association plots for the most significant SNP (by outcome and epoch, as listed in Table 2) are shown in Figure IV in the Data Supplement. Regional association plots for SNP clusters are presented in Figure V in the Data Supplement (SBP) and Figure VI in the Data Supplement (DBP). Regional association plots and linkage disequilibrium plots for significant SNP clusters for SBP and DBP are presented by epoch in Figures VII to IX in the Data Supplement. Forest plots for all significant SNP clusters and most significant association by outcome and epoch are presented in Figures X to XV in the Data Supplement. Overview figures (forest plot, regional association plot, and Manhattan plot) are presented by epoch and outcome in Figures XVI to XVIII in the Data Supplement. Plots relating to the Encyclopedia of DNA Elements functionality are displayed in Figures XIX to XXII in the Data Supplement. Descriptive characteristics of each cohort are detailed in Table II in the Data Supplement. Summary of known BP (and BP-related effects) for significant genes and variants associated from EAGLE are shown in Tables III and IV in the Data Supplement and ICBP in Tables V and VI in the Data Supplement. Comparison of EAGLE meta-analysis results with CARDIOGRAM are in given in Table VII in the Data Supplement. Top SNP clusters are summarized in Tables VIII and IX in the Data Supplement. Comparisons between EAGLE and ICBP are given in Tables X and XI in the Data Supplement. Comparing significant SNPs from sex-stratified meta-analyses to single cohort analyses with sex by SNP interactions are described in Table XII in the Data Supplement. Comparing meta-analyses across epochs for EAGLE are detailed in Tables XIII to XIV in the Data Supplement. Summary of known BP (and BP-related effects) for significant genes and variants associated with multiple epochs are listed in Tables XV and XVI in the Data Supplement.

Systolic Blood Pressure

Genome-Wide Significance

Two SNPs reached genome-wide levels of significance ($P<5\times10^{-8}$) for childhood SBP (Table 2): in the prepubertal epoch, rs1563894 (chromosome position, 15.66422829; gene, *ITGA11*; per allele mean difference in SBP =–0.093SD [95% CI: –0.126, –0.060]; $P=2.86\times10^{-8}$; Tables 2 and 3 and Figures VI and XV in the Data Supplement); and during the pubertal epoch, rs872256 (chromosome position, 9.2496480; gene, unknown; β=0.096SD [95% CI: 0.063, 0.129]; $P=8.67\times10^{-9}$; Table 2). No SNPs reached genome-wide levels of significance for SBP in the postpubertal analyses.

Clusters of variants in several genes were associated with SBP at $P \leq 5\times10^{-3}$ (Table 3, Figure 1, and Figure V in the Data Supplement): *ITGA11* (prepuberty), *ANLN* and *OR51V1* (puberty), and *C1GALT1* and *UGP2* (postpuberty). A cluster of SNPs was also identified surrounding SNP rs1563894 (*ITGA11*; prepuberty), highlighted above as showing genome-wide levels of significance with prepubertal SBP. We illustrate this significant SNP cluster in more depth (Figure 2).

Two SNPs were associated with the largest increases in SBP across these epochs: SNP rs3735398 (*ANLN*) during the pubertal epoch (β=0.116SD, 95% CI, 0.073, 0.159; $P=1.28\times10^{-7}$; Table 3 and Figure VIII in the Data Supplement) and a cluster surrounding SNP rs3901287 (*LOXL2*; β=0.108SD, 95% CI, 0.059, 0.157; $P=1.24\times10^{-5}$; Table 3 and Figure IX in the Data Supplement) was associated with postpubertal SBP.

Look-Up of Functionality of Childhood SBP Results

Several SNPs were found to be located either directly in or in close proximity to functionally active regions. For SNPs associated with SBP, rs1563894 was located on an active H3K27Ac, DNase hypersensitivity, transcription factor ChIP, and CpG methylation site (Figure 3 and Figure XIXa in the Data Supplement). Rs1010366 was located downstream and in close proximity to densely active H3K27Ac, DNase hypersensitivity, transcription factor ChIP, and CpG methylation site (Figure XIXc in the Data Supplement). Rs3735398 was located in a region of active transcription and DNase hypersensitivity. Rs3787159 was located directly upstream from areas with active transcription DNase hypersensitivity and transcription factor ChIP (Figure XXIb in the Data Supplement). Rs4538187 was located in a region of transcription factor ChIP and methylation and upstream from an active transcription site and downstream from an active H3K27Ac mark with dense methylation and transcription factor active H3K27Ac mark, DNase hypersensitivity, transcription factor ChIP, and CpG methylation site, whereas rs3901287 was located in close proximity to areas of active transcription, H3K27Ac mark, DNase hypersensitivity, transcription factor ChIP, and methylation (Figure XXIc in the Data Supplement).

Comparisons Across Epochs and With Adult Outcomes

No SNPs reached associations of $P \leq 5\times10^{-3}$ in all 3 epochs. Variants in chromosome 2 (rs13025174, rs13032473 [*TMEM247*], and rs10186089 [*FSHR*]) were associated with elevated SBP during prepubertal and pubertal epochs (Table 4). Several SNPs

Table 2. Most Significant Findings per Time Frame, Data Set, and BP Outcome Measure (Sex-Combined)

	SBP		DBP	
Time Frame	SNPs $<5\times10^{-8}$	Most Significant Finding	SNPs $<5\times10^{-8}$	Most Significant Finding
Prepuberty	1	rs1563894	0	rs13040824
		Beta=−0.093		Beta=−0.902
		95% CI=[−0.126, −0.060]		95% CI=[−0.127, −0.054]
		$P=2.86\times10^{-8}$		$P=9.33\times10^{-7}$
		Chromosome: 15		Chromosome: 20
		Gene: ITGA11		Gene: Unknown
		Nearby genes: FEM1B, CORO2B, CALML4		Nearby genes: None
		MAF=0.19		MAF=0.30
		$\hat{R}^2$ range =[0.67, 0.96]		$\hat{R}^2$ range =[0.49, 0.99]
Puberty	1	rs872256	0	rs7897969
		Beta=0.096		Beta=−0.749
		95% CI=[0.063,0.129]		95% CI=[−1.001, −0.496]
		$P=8.67\times10^{-9}$		$P=4.82\times10^{-7}$
		Chromosome: 9		Chromosome: 10
		Gene: Unknown		Gene: Unknown
		Nearby genes: SMARCA2, VLDLR		Nearby genes: None
		MAF=0.41		MAF=0.15
		$\hat{R}^2$ range =[0.94, 0.95]		$\hat{R}^2$ range =[0.09, 0.48]
Postpuberty	0	rs1010366	0	rs12365302
		Beta=0.098		Beta=0.139
		95% CI=[0.057,0.139]		95% CI=[0.086,0.192]
		$P=3.31\times10^{-6}$		$P=3.96\times10^{-7}$
		Chromosome: 7		Chromosome:11
		Gene: C1GALT1		Gene: Unknown
		Nearby genes: None		Nearby genes: SLC35C1, CHST1
		MAF=0.39		MAF=0.17
		$\hat{R}^2$ range =[0.97, 0.99]		$\hat{R}^2$ range =[0.97, 0.98]

CI indicates confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

The sum of the number of SNPs reaching genome-wide levels of significance ($P\leq5\times10^{-8}$) where all SNPs had an MAF>0.10 and all cohorts contributed to each SNP analyses (postpubertal) and at least 4 cohorts contributed to GWAS findings for the prepubertal and pubertal epochs. Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

in *HORMAD2*, *HORMAD2-AS1*, and *MTMR3* were associated with SBP during the pubertal and postpubertal epochs (Table 4 and Table XIII in the Data Supplement).

None of the SNPs found to be associated ($P\leq5\times10^{-3}$) with childhood SBP were associated with adult SBP in the ICBP (Table 3). However, several loci previously found to be associated with adult SBP in ICBP were also associated with SBP in at least one epoch of childhood in EAGLE children (Table 5): (1) *B3GNTL1* and *KLHL1* (prepuberty); (2) *DOK6*, *NKAIN2*, *ARGHGEF10*, and *MECOM* (puberty) and (2) *FGD5* and *CSMD2* (postpuberty). One SNP that was associated with SBP in the pubertal epoch showed some possible association with CHD in adults (Table VII in the Data Supplement; rs3735398; P=0.039).

Diastolic Blood Pressure

Genome-Wide Significance

No SNPs reached genome wide levels of significance ($P<5\times10^{-8}$) for childhood DBP (Table 2).

Clusters of variants in 7 loci were associated with childhood DBP ($P\leq5\times10^{-3}$; Table 3) and were investigated further using LocusZoom.[40] Regional associations for all of these associations are presented in Figure VI in the Data Supplement. SNPs associated with the largest positive increases in DBP per epoch included a prepubertal epoch cluster led by rs1714524 (*LOC100996447*; β=0.154SD, 95% CI, 0.081, 0.227; $P=8.32\times10^{-5}$; Figure 2 and Figure VIa in the Data Supplement). For the pubertal epoch, a cluster led by rs1387977 (*TRHDE*; β=0.127SD, 95% CI, 0.064,

Table 3. Top SNP Clusters From Systolic Blood Pressure and Diastolic Blood Pressure Meta-Analyses in EAGLE for Sex-Combined Data Sets

Time Frame	Marker Name	Allele	CHR	POS	MAF	Gene	Beta (95% CI)	*P* Value	Direction	ICBP *p*	N Effective
Systolic blood pressure											
Prepubertal	rs1563894	A/G	15	66422829	0.19	ITGA11	–0.093 (–0.126, –0.060)	2.86E-08*	−−−−−	0.46	10090
Pubertal	rs3735398	A/G	7	36412646	0.12	ANLN	0.116 (0.073,0.159)	1.28E-07	+++++	0.75	8423
	rs3787159	T/C	20	56252573	0.46	PPP4R1L	–0.064 (–0.091, –0.037)	8.76E-06	−−+−−	0.46	8423
	rs9667878	T/C	11	5180326	0.22	OR51V1	0.135 (0.0740,0.196)	9.74E-06	+++++	1.00	8423
Postpubertal	rs1010366	T/C	7	7196351	0.39	C1GALT1	0.098 (0.057,0.139)	3.31E-06	−++	0.90	5176
	rs4538187	A/G	2	63957245	0.16	UGP2	0.102 (0.057,0.147)	5.96E-06	+++	0.70	5176
	rs3901287	A/T	8	23240509	0.28	LOXL2	0.108 (0.059,0.157)	1.24E-05	+++	0.68	5176
Diastolic blood pressure											
Prepubertal	rs241264	T/C	1	4518898	0.31	Between LOC284661 and AJAP1	–0.082 (–0.0120, –0.043)	2.95E-05	−−−−−	0.48	10090
	rs1714524	T/C	3	159755790	0.44	LOC100996447	0.154 (0.081,0.227)	8.32E-05	−−−−+	0.99	10090
	rs16875222	A/T	8	107955966	0.11	Near ABRA, OXR1	–0.119 (–0.179, –0.060)	8.21E-05	−−−−−	0.72	8423
	rs12237240	T/G	9	28329306	0.19	LINGO2	0.068 (0.034,0.102)	8.71E-05	++−+−	0.89	8423
	rs1387977	T/G	12	71307607	0.14	TRHDE	0.127 (0.064,0.190)	6.92E-05	++−++	0.90	8423
Postpubertal	rs6949619	T/C	7	24396900	0.19	Near NPY	–0.092 (–0.133, –0.051)	1.13E-05	−−−	0.45	5176
	rs229038	C/G	21	27127300	0.22	ADAMTS1	0.213 (0.115,0.311)	2.26E-05	+++	0.77	5176

Bold text highlights SNPs ($P<5\times10^{-3}$) represented in regional association plots shown in Figures VII–IX in the Data Supplement. Beta values are in terms of Z-scores, the number of standard deviations away from the mean. CHR indicates chromosome; MAF, minor allele frequency; and POS, position.

*SNPs which have reached genome-wide levels of significance ($P<5\times10^{-8}$).

0.190; $P=6.92\times10^{-5}$; Figure VIb in the Data Supplement). For the postpubertal epoch, a cluster led by rs6949619 (*gene unknown, near NPY*; β=–0.092SD, 95% CI, –0.133, –0.051; $P=1.13\times10^{-5}$; Figure VIc in the Data Supplement).

Look-Up of Functionality of Childhood DBP Results

For SNPs associated with DBP, rs13040824 was located downstream from an active H3K27Ac mark and located between 2 regions of DNase hypersensitivity and transcription factor ChIP (Figure XXa in the Data Supplement). Rs7897969 was located between 2 regions that had high levels of DNase hypersensitivity, transcription factor ChIP, and methylation (Figure XXb in the Data Supplement). Rs1236530 was located in a region of DNase hypersensitivity and transcription factor ChIP (Figure XXc in the Data Supplement). Rs241264 was located between 2 areas of high methylation, whereas rs1714524 was located in an area of active transcription (Figure 3 and Figure XXIIa in the Data Supplement). Rs1687522 was located in an area of active transcription and methylation (Figure XXIIb in the Data Supplement). Rs229038 was located within a cluster of DNase hypersensitivity and upstream for a highly active region of transcription and regulation (Figure XXIIc in the Data Supplement).

Look-Up of DBP Results Across Epochs in Childhood/Adolescence

No SNPs were significantly associated ($P\leq5\times10^{-3}$) with DBP across all epochs. Opposing effects were observed for rs13004438 (*CCDC141*) for increasing DBP (β=0.082SD, 95% CI, 0.034, 0.13; $P=8.31\times10^{-4}$) during the prepubertal epoch but reducing it during the pubertal epoch (β=–0.053SD, 95% CI, –0.115, –0.030; $P=8.10\times10^{-4}$; Table 4). Variants in *POT1* and *CNTNAP4* were associated with consistently reducing DBP during the pubertal and postpubertal epochs (Table 4 and Table XIV in the Data Supplement).

None of the SNPs found to be at least associated ($P\leq5\times10^{-3}$) with childhood DBP were associated with adult BP in the ICBP (Table 4). A number of loci previously found to be associated with adult DBP in ICBP were also associated with DBP in at least one epoch of childhood in EAGLE children (Table 5): *USP4* and *GRK5* (all pubertal).

We also investigated SNPs from Tables 2 and 3 in CARDIoGRAMplusC4D[36] and found 2 significant hits for rs12365302 ($P=0.008$) and rs16875222 ($P=0.037$; Table VII in the Data Supplement).

Additional Analyses

As a sensitivity analyses, we repeated the GWAS analyses separately in females and males and found similar directions and magnitudes of associations, though given the smaller sample sizes within these 2 subgroups were not as well powered to report on the sex-stratified associations (Tables VIII–XII in the Data Supplement).

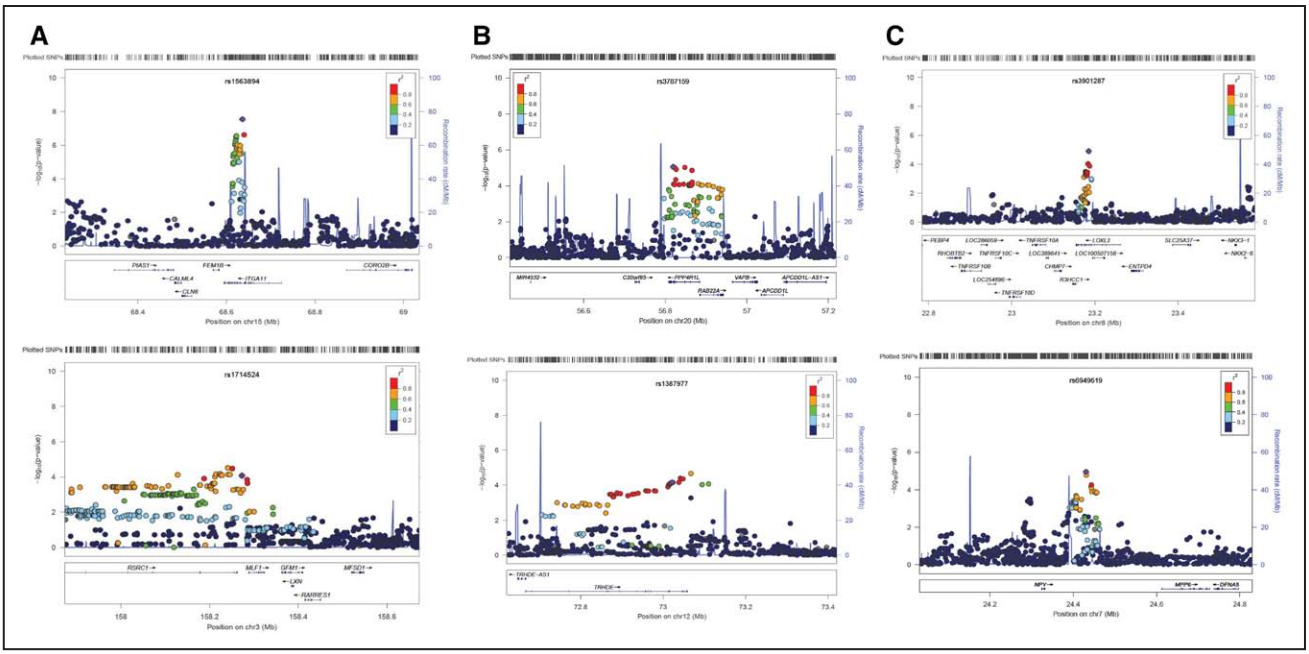

Figure 1. Regional association plots for significant SNP clusters –log10 (*P* values) are shown for all SNPs in the region, and color of circles indicates degree of LD with the most associated SNP in the region. SNPs correspond to those highlighted in bold text in Table 3. Plots shown on left represent systolic blood pressure, plots shown on right represent diastolic blood pressure. Rows represent prepubertal (**A**), pubertal (**B**), and postpubertal (**C**). For regional association, plots for all significant SNP clusters presented in Table 4 refer to Figures VII and VIII in the Data Supplement. LD indicates linkage disequilibrium.

Discussion

To our knowledge, this is the first GWAS to examine genetic associations with BP cross-sectionally across childhood and adolescence. This builds on our previous work in which we found that an allelic score summing the established adult GWAS hits for SBP was associated with SBP at mean age 6 years but not with age-related change in SBP between age 6 and 17.[41,42] In the current study, we have identified 2 novel SNPs: one associated with SBP measured prepubertally and one with SBP measured during puberty. We did not find any SNPs reaching genome-wide significance with DBP or with either SBP- or DBP-measured postpuberty, but when we reduced our statistical significance threshold to $P \leq 5\times10^{-3}$, there were several additional variants in gene clusters relating to SBP or DBP across the 3 epochs. At this more liberal *P* value threshold, we found some evidence of overlap in novel SNPs across childhood/adolescent age epochs within our study and some overlap with those that have been found by previous GWAS to be associated with adult BP.

ITGA11 was genome-wide associated with SBP during the prepubertal epoch and has been shown to be associated with hypertrophic cardiomyopathy[43] and coronary artery disease.[44] An SNP in close proximity to the *SMARCA* and *VLDLR* genes (rs872256) was genome-wide associated with SBP during the pubertal epoch. *SMARCA* is a member of the *SWI/SNF* family of proteins and is highly similar to the brahma protein, where it has been hypothesized that cardiac hypertrophy and the fetal gene expression program are associated with distinguishable binding of brahma and *SMARCA4* on genes.[45] From animal studies, brahma gene expression is found to be restricted to mesodermal tissues involved in early vasculogenesis and heart morphogenesis.[46] *VLDLR* has been shown to be associated with obesity from both animal studies[47–49] and human GWAS.[50] Recently, a pathway analyses based on results from a GWAS has identified plausible biological links between *VLDR* with vascular endothelial growth factor, which is known to affect angiogenesis and atherosclerosis.[51] Even with a reduced *P* value threshold of $P \leq 5\times10^{-3}$, these 2 genome-wide novel variants did not overlap with variants at this threshold in any other age group.

Some of the variants that we identified as associated with SBP or DBP in any of the different age epochs were in gene clusters that also had some evidence of potentially relevant functionality. *FSHR* which was associated with SBP in prepubertal and puberty has been shown to influence SBP vascular responses in hypertensive rats with hyperhomocysteinemia[52] and is known to be involved in the regulation of systemic arterial BP (GeneCards). *POT1* which was associated with lower DBP in pubertal and postpubertal children is an important molecular marker for biological aging.[53] *MTMR3* which was associated with lower SBP in puberty and postpuberty has been hypothesized to be a mediator for miR-4513, which is significantly associated with BP and related metabolic outcomes, such as cholesterol.[54]

The fact that we have found more variants associated with SBP than with DBP may reflect differences in changes in SBP and DBP across childhood and adolescence. SBP increases across childhood to a peak at around age 15/16 years and thereafter levels off, whereas DBP seems to increase monotonically across childhood into late adolescence/early twenties.[26,27] This is the first GWAS of BP in children at different ages, and we have maximized the sample size by collaborating across several studies with relevant data. We limited analyses

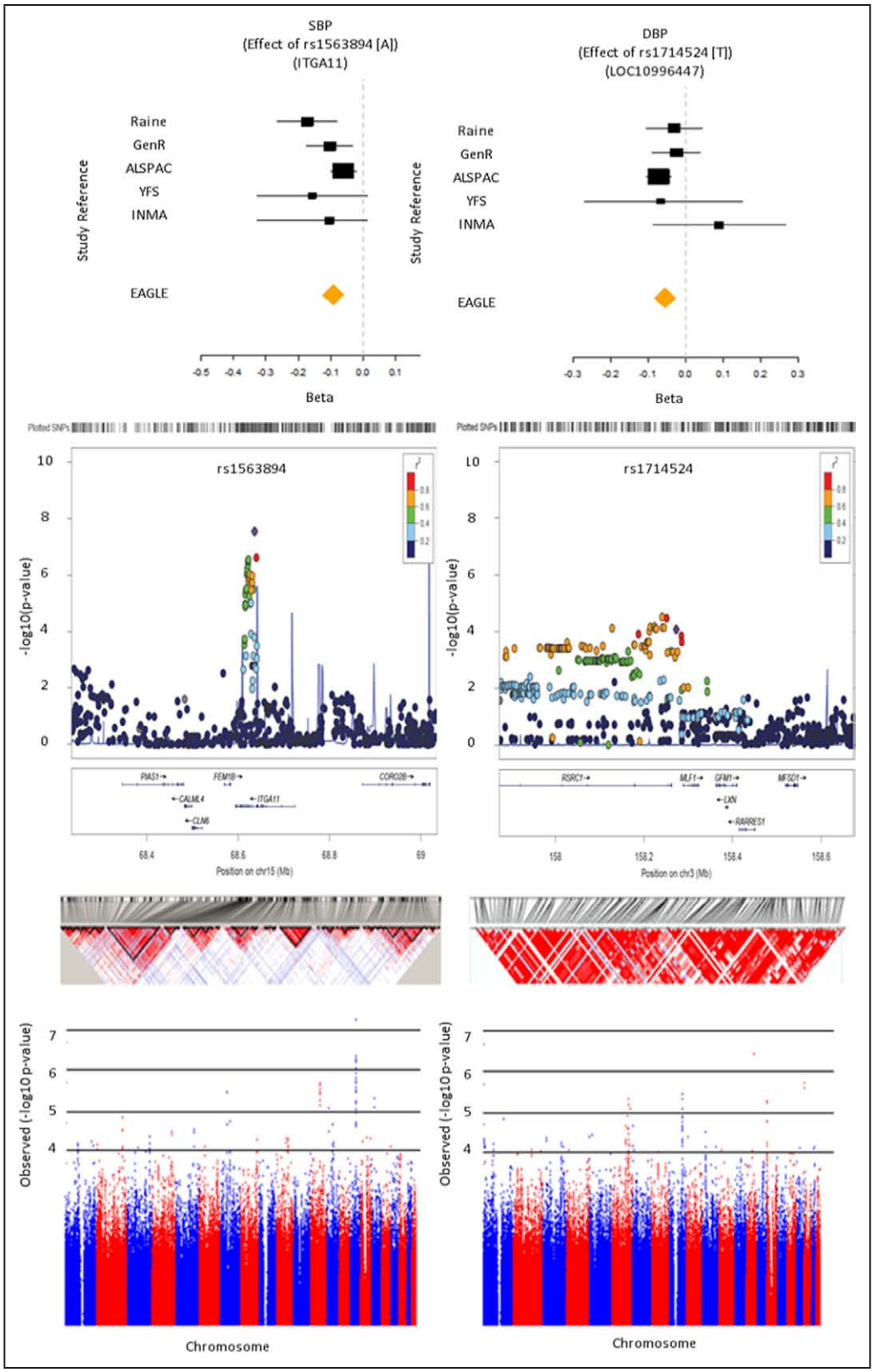

Figure 2. Most significant SNP clusters resulting from the sex-combined meta-analyses genome-wide association study (GWAS). From top to bottom: forest plot, regional association plot (–log10 (*P* values)), linkage disequilibrium plots (LOD scores), and Manhattan plots (–log10 (*P* values)). Green boxed areas on Manhattan plots highlight chromosome regions illustrated in regional association plots. Letters signify the following data subsets: SBP (**A**) and DBP (**B**) for the prepubertal epoch. ALSPAC indicates The Avon Longitudinal Study of Parents and Children Bristol, UK; EAGLE< Early Genetics and Lifecourse Epidemiology; GenR, The Generation R Study Group, Rotterdam, The Netherlands; ICBP, International Consortium of Blood Pressure; INMA, Spanish INMA—Infancia y Medio Ambiente, Barcelona, Catalonia, Spain; Raine, The Western Australian Pregnancy (Raine) Cohort, Perth, Western Australia; YFS; The Cardiovascular Risk in Young Finns Study, Turku, Finland.

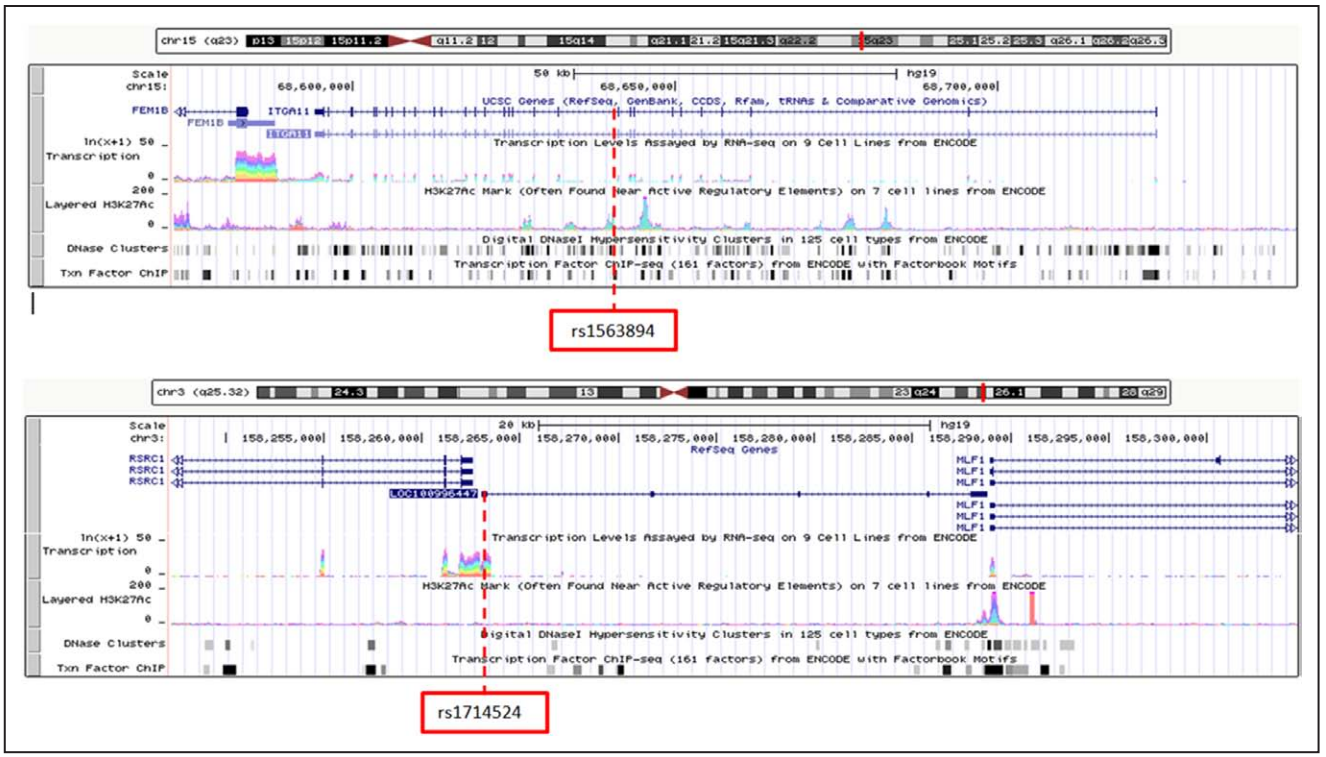

Figure 3. An overview of the Encyclopedia of DNA Elements functional activity (transcriptional active region, H3K27Ac active regulatory elements, DNase hypersensitivity transcription factor–binding site information from chromatin immunoprecipitation [ChIP] analysis, and CpG methylation levels) for rs1563894 (**A**; SBP) and rs1714524 (**B**; DBP) during the prepubertal epoch.

to Europeans only to minimize population stratification and followed-up hits by looking up for functionality and for overlap with SNPs from GWAS in adults.

We used age groups to define epochs during which BP was measured as prepubertal, pubertal, and postpubertal. We acknowledge that some participants will have been incorrectly categorized by this method. However, it was not possible to use Tanner scores for all participants, and to have used those data would have compromised our sample size. Furthermore, assessment of pubertal stages using self- (or parental) assessment of Tanner scales, which were the methods used in most cohorts in EAGLE, is also prone to misclassification.[55] Misclassification because of using age is likely to be random, whereas Tanner scores could be systematic in relation to characteristics, such as body mass, that are related to BP.

Our sample size was too small to definitely test for sex differences, but consistent with findings from adult GWAS[17,20,55–57]; there did not seem to be notable differences between females and males. In many of our analyses, we used a *P* value threshold that was larger than conventional genome-wide thresholds. This decision was made a priori and was intended to ensure that we did not miss potentially important associations and overlaps (between epochs and with adult GWAS findings) given the relatively modest sample size. However, we acknowledge that these findings should be treated with caution until they are replicated.

Conclusions

To conclude, we have identified 2 novel loci related to SBP in childhood (one at prepuberty and one during puberty), but none related to SBP postpuberty or in any age epoch for DBP in childhood, at genome-wide significance. The 2 novel SBP SNPs were specific to those epochs and did not relate to SBP in other epochs even with a higher *P* value threshold of $P \leq 5 \times 10^{-3}$. With this more liberal *P* value, we identified more variants related to SBP and 2 variants related to DPB measured during puberty. Most of these were specific to the particular epoch in which they were found, though for a small number, we did find overlap with adjacent epochs and also some overlap with published adult variants. Thus, our results provide some support for age-specific associations, as well as for associations that might be present across most ages. The observed genetic associations with no previous history of association with adult BP may be true novel associations, but require further investigation and replication.

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Table 4. Comparing SBP and DBP Meta-Analyses Across Epochs in EAGLE

Marker Name	CHR	POS	Gene	MAF	Allele	Prepubertal			Pubertal		
						Beta (95% CI)	*P* Value	Direction	Beta (95% CI)	*P* Value	Direction
Systolic blood pressure											
rs13025174	2	46557999		0.56	A/G	0.075 (0.031,0.12)	9.37E-04	++++	0.054 (0.026,0.082)	1.38E-04	++−++
rs13032473	2	46559169	TMEM247	0.56	A/G	0.076 (0.031,0.121)	8.60E-04	++++	0.054 (0.026,0.082)	1.38E-04	++−++
rs10186089	2	49072628	FSHR	0.83	A/G	0.123 (0.056,0.190)	3.07E-04	++++	0.073 (0.031,0.114)	5.45E-04	++−−+
						Pubertal			Postpubertal		
rs1383450	8	56167423		0.87	T/C	0.073 (0.033,0.112)	2.85E-04	+++++	0.115 (0.063,0.167)	1.47E-05	?++
rs276978	16	84783954		0.30	T/C	0.073 (0.030,0.117)	9.88E-04	−++−+	0.098 (0.043,0.153)	5.26E-04	+++
rs2239382	20	9449526	LAMP5	0.25	C/G	−0.069 (−0.108, −0.030)	5.62E-04	−−+−−	−0.083 (−0.131, −0.035)	7.33E-04	−−−−
rs5752974	22	28601630		0.96	A/G	−0.088 (−0.137, −0.040)	3.74E-04	−−++−	−0.115 (−0.175,-0.055)	1.79E-04	−−−
rs16988143	22	28704677	MTMR3	0.04	T/C	0.09 (0.041,0.138)	3.05E-04	++−−+	0.118 (0.057,0.179)	1.61E-04	+++
rs11552852	22	28754377	HORMAD2-AS1, MTMR3	0.98	T/C	−0.093 (−0.142, −0.043)	2.68E-04	−−++−	−0.123 (−0.185, −0.062)	7.87E-05	−−−
rs16988244	22	28763373	HORMAD2-AS1	0.04	T/G	0.091 (0.042,0.140)	2.46E-04	++−−+	0.115 (0.055,0.175)	1.71E-04	+++
rs16988333	22	28882813	HORMAD2	0.04	A/G	0.090 (0.041,0.139)	2.84E-04	++−−+	0.110 (0.050, 0.170)	3.12E-04	+++
rs5753042	22	28917972	HORMAD2, LOC105372988	0.06	A/G	0.088 (0.039,0.137)	3.92E-04	++−−+	0.105 (0.044,0.167)	7.64E-04	+++
Diastolic blood pressure											
rs13004438	2	179421913	CCDC141, LOC105373766	0.17	T/C	0.082 (0.034,0.13)	8.31E-04	+++	−0.053 (−0.084, −0.022)	8.10E-04	−−−−−
						Prepubertal			Postpubertal		
rs12542146	8	10485173		0.23	A/G	0.100 (0.041,0.159)	9.29E-04	++?	−0.073 (−0.115, −0.030)	8.42E-04	−−−
rs9373002	6	132279972		0.28	A/G	0.101 (0.042,0.159)	7.36E-04	++?	0.072 (0.029,0.114)	8.95E-04	+++
						Pubertal			Postpubertal		
rs2944782	2	47750478		0.21	A/G	0.075 (0.033,0.117)	4.35E-04	+++++	0.090 (0.041,0.140)	3.31E-04	+++
rs12532038	7	124281701	POT1	0.39	T/C	-0.059 (−0.090,-0.028)	2.06E-04	—-+	−0.067 (−0.106, −0.028)	8.25E-04	−−+
rs734335	14	100648711		0.40	A/G	−0.092 (−0.136, −0.047)	5.23E-05	−−−−−	−0.110 (−0.165, −0.055)	9.20E-05	−−−
rs8044400	16	74923996	CNTNAP4	0.84	T/C	−0.116 (−0.164, −0.068)	2.10E-06	−−−−+	−0.099 (−0.157, −0.040)	9.17E-04	−−−

Beta values are in terms of Z-scores, the number of standard deviations away from the mean. CI indicates confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

area, Rotterdam; the Rotterdam Homecare Foundation, Rotterdam; and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam. The generation and management of GWAS genotype data for the Generation R Study were done at the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, The Netherlands. We thank Karol Estrada, Dr Tobias A. Knoch, Anis Abuseiris, Luc V. de Zeeuw, and Rob de Graaf for their help in creating GRIMP, BigGRID, MediGRID,

Table 5. Comparing Systolic and Diastolic Blood Pressure Meta-Analyses in Childhood (EAGLE) and Adulthood (ICBP) for Sex-Combined Data Sets

						ICBP		EAGLE	
Time Frame	Marker Name	CHR	POS	Gene	MAF	Beta	*P* Value	Beta (95%CI)	*P* Value
Systolic blood pressure									
Prepubertal	rs4986146	17	78534809	B3GNTL1	0.3	0.422 (0.157,0.686)	1.77E-03	−0.055 (−0.086, −0.024)	5.98E-04
	rs17810777	13	69385636	KLHL1	0.11	0.377 (0.127,0.628)	3.17E-03	0.066 (0.031,0.101)	2.05E-04
Pubertal	rs8096788	18	65451861	DOK6	0.31	0.65 (0.299,1.001)	2.80E-04	−0.095 (−0.146, −0.044)	2.61E-04
	rs38627	7	76275543		0.27	0.495 (0.209,0.782)	6.89E-04	0.077 (0.034,0.120)	3.72E-04
	rs4943826	11	80730697		0.23	0.459 (0.163,0.755)	2.36E-03	0.075 (0.032,0.118)	5.65E-04
	rs332607	6	124765053	NKAIN2	0.25	0.317 (0.106,0.528)	3.19E-03	0.054 (0.025,0.083)	3.55E-04
	rs3824137	8	1808899	ARHGEF10	0.23	0.358 (0.115,0.601)	3.87E-03	0.058 (0.023,0.093)	9.13E-04
	rs11711274	3	170597773	MECOM	0.01	1.404 (0.437,2.371)	4.42E-03	−0.400 (−0.606, −0.194)	1.40E-04
	rs17033041	4	156610757		0.14	0.375 (0.116,0.633)	4.47E-03	−0.066 (−0.105, −0.027)	9.66E-04
Postpubertal	rs293927	3	14907160	FGD5	0.13	0.422 (0.183,0.661)	5.42E-04	−0.082 (−0.125, −0.039)	2.06E-04
	rs1687304	3	14929257	FGD5	0.13	0.404 (0.164,0.645)	9.75E-04	0.089 (0.046,0.132)	6.21E-05
	rs625757	1	33922472	CSMD2	0.07	0.601 (0.261,0.942)	5.43E-04	−0.104 (−0.163, −0.045)	4.93E-04
Diastolic blood pressure									
Prepubertal	rs6760458	2	42938973		0.23	0.195 (0.06,0.329)	4.63E-03	0.055 (0.022,0.088)	8.67E-04
Pubertal	rs7578149	2	20175919		0.46	0.213 (0.087,0.339)	9.08E-04	−0.050 (−0.079, −0.021)	9.83E-04
	rs11713251	3	49315011	USP4	0.01	0.81 (0.292,1.327)	2.19E-03	0.213 (0.093,0.333)	5.03E-04
	rs7914808	10	120991173	GRK5	0.31	0.344 (0.108,0.579)	4.20E-03	0.091 (0.038,0.144)	9.07E-04
	rs1951930	6	33890633		0.15	0.218 (0.059,0.376)	7.15E-03	0.066 (0.027,0.105)	7.49E-04
Postpubertal	rs4650447	1	80256759		0.41	0.205 (0.081,0.328)	1.18E-03	−0.063 (−0.100, −0.026)	9.63E-04
	rs17064088	5	174293917		0.05	0.415 (0.142,0.689)	2.90E-03	0.122 (0.051,0.193)	6.71E-04

Please note that the International Consortium of Blood Pressure (ICBP) released their GWAS results here: http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000585.v1.p1; however, the effects reported (beta) are absolute values of the regression coefficient. Beta values are in terms of Z-scores, the number of standard deviations away from the mean. EAGLE, Early Genetics and Lifecourse Epidemiology; and ICBP, International Consortium of Blood Pressure.

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Appendix

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CLINICAL PERSPECTIVE

This study was designed to identify genetic variants associated with blood pressure in childhood and adolescence to improve our understanding of the lifecourse pathogenesis of hypertension and cardiovascular disease. Variation in systolic and diastolic blood pressure across the lifecourse is associated with subsequent adult risk of coronary heart disease and stroke. The age-related changes in blood pressure in industrialized countries suggest a varying gene environment interaction with age, but to date, relatively little is known about the genetic determinants of blood pressure in childhood and adolescence. Two novel loci were identified as having genome-wide associations with systolic blood pressure in specific age epochs. These loci were rs1563894 [*ITGA11*], associated with systolic blood pressure assessed prepuberty, and rs872256, which was associated with blood pressure during puberty. *ITGA11* has been shown to be associated with hypertrophic cardiomyopathy and coronary artery disease. Rs872256 is in close proximity to the *SMARCA* and *VLDLR* genes. *SMARCA* is thought to influence cardiac hypertrophy and fetal gene expression. *VLDLR* has been shown to be associated with obesity and has plausible biological links with angiogenesis and atherosclerosis. We also found some evidence of gene clusters associated with blood pressure in childhood. Most of the effects we observed were specific to the particular epoch in which they were found, though a small number overlapped with adjacent epochs and with published adult variants. Our results suggest that genetic determinants of blood pressure act from childhood, develop over the life course, and show some evidence of age-specific effects.

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International Genome-Wide Association Study Consortium Identifies Novel Loci Associated With Blood Pressure in Children and Adolescents

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Supplemental Material

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Population-based GWAS samples and phenotype measurements

The EArly Genetics and Lifecourse Epidemiology (EAGLE) Consortium is an international consortium of pregnancy and birth cohorts that aims to collaborate to investigate the genetic basis of phenotypes in antental and early life and childhood. EAGLE covers a broad range of pathways and phenotypes, integrating closely with the DOHaD (developmental origins of health and disease) community. Further details can be found here: http://research.lunenfeld.ca/eagle/. Descriptions for each cohort that participated in this study are detailed here. All participants provided written informed consent and studies were approved by local Research Ethics Committees and/or Institutional Review boards.

Participating Study Cohort Descriptions

Raine

*The Western Australian Pregnancy (**Raine**) Cohort, Perth, Western Australia*

Recruitment of the Western Australian Pregnancy (Raine) cohort has previously been described in detail[1]. Between 1989 and 1991 2,900 pregnant women were recruited at King Edwards Memorial Hospital (Perth, WA) prior to 18-weeks gestation into a randomized controlled trial to evaluate the effects of repeated ultrasound in pregnancy. The study was conducted with appropriate institutional ethics approval, and written informed consent was obtained from mothers at all follow-ups and participants at the year 17 follow-up. Further details about this study can be found at the study website http://www.rainestudy.org.au/.

BP was measured on individuals who rested in a seated position for 5 minutes. Right arm circumference was measured and the appropriate cuff size was used. Measurements were recorded T 1, 2, 3, 5, 8, 10, 12, 14 and 17 years using an oscillometric sphygmomanometer (DINAMAP vital signs monitor 8100, DINAMAP XL vital signs monitor, or DINAMAP ProCare 100) automating readings per 2 minute intervals.

For each participant we took a measure of BP from any clinic relevant to each epoch to maximise participation and sample size. This cohort contributes to the following epochs: pre-pubertal (N = 1056, mean age = 5.9 years) and pubertal (N = 1055, mean age = 10.6 years) and post-puberty (N = 1160, mean age = 17.0 years). For data collected during the pre-pubertal and pubertal epochs three recordings were taken. Six recordings were taken during the post-pubertal epoch. The first BP measure was discarded and the mean of the remaining measures was converted to a Z-score used in GWAS analyses.

DNA was collected at the year 14 (74% of all adolescents) and year 17 (additional 5% of all adolescents) follow-ups using standardized procedures. High throughput genome-wide SNP genotyping using the genome-wide Illumina 660 Quad Array was performed for each individual. Genotype data were imputed against Hapmap phase2 build 36 release 22 using MACH v1.0.16 after quality control (MAF>1%, HWE>$5x10^{-7}$, call rate per SNP and person >95%). Genome-wide association analysis of the SBP and DBP phenotype was carried out in MACH2DAT. Principal components analysis of genome-wide SNP data with Eigenstrat[2] has revealed evidence of population stratification in the Raine sample, and so the first two principal components were included as cofactors in all analyses. This procedure has been used previously in genetic analyses of the Raine cohort [3, 4].

Generation R

*The **Gen**eration **R** Study Group, Rotterdam, The Netherlands*

The Generation R Study is a population-based prospective cohort study from fetal life until childhood. All children were born between April 2002 and January 2006. This study is designed to identify early environmental and genetic determinants of growth, development and health from fetal life until young adulthood and has been described previously in detail [5, 6].The study has been approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all participants or their parent(s). Further details about this study can be found at the study website http://www.generationr.nl/.

The child was lying quietly, while systolic and diastolic blood pressure was measured at the right brachial artery in supine position, four times with one minute intervals, using the validated automatic sphygmanometer Datascope Accutor Plus ™ (Paramus, NJ, USA)[7]. Blood pressure measurements in childhood were performed in a dedicated research centre in the Erasmus Medical Center, Rotterdam, the Netherlands. A cuff was selected with a cuff width approximately 40% of the arm circumference and long enough to cover 90% of the arm circumference. More than 90% of the children who visited the research centre had four successful blood pressure measurements available. The first blood pressure measure was discarded and the mean of the remaining measures were converted to a Z-score used in GWAS analyses. Analyses were restricted to Caucasian individuals with genome-wide data and blood pressure measurements available. This cohort contributes to the pre-pubertal (n=1847 mean age = 6.09 years).

Cord blood for DNA isolation was available in 59% of all live-born participating children. Sex-mismatch rate between genome based sex and midwives' record based sex was low (<0.5%), indicating that possible contamination of maternal DNA was extremely low. Missing cord blood samples were mainly due to logistical constraints at the delivery. Individual genotype data were extracted from the genome-wide Illumina 610 Quad Array. Genotype data were imputed against Hapmap phase2 build 36 release 22 using MACH after quality control (MAF>1%, HWE>$1x10^{-6}$, call rate per SNP and person >95%). Genome-wide association analysis of the systolic and diastolic blood pressure phenotype was carried out in MACH2QTL.

ALSPAC

*The **A**von **L**ongitudinal **S**tudy of **P**arents and **C**hildren Bristol, UK*

ALSPAC is a longitudinal population-based birth cohort that recruited pregnant women residing in Avon, in the South West of the UK, with an expected delivery date between 1st April 1991 and 31st December 1992. Ethical approval was obtained from the ALSPAC Law and Ethics committee and relevant local ethics committees. The cohort, including its representativeness, is described in detail on the website http://www.alspac.bris.ac.uk and elsewhere[8, 9].

At each clinic, SBP and DBP were measured twice with the child sitting and at rest with their arm supported, using a cuff size appropriate for the child's upper arm circumference. The mean of the two measures is used in our analyses. A Dinamap 9301 Vital Signs Monitor (Morton Medical, London) was used at the 7, 9 and 11 year clinics and a Dinamap 8100 Vital Signs Monitor (Morton Medical, London) was used at the 13, 15 and 17 year clinics. A maximum of 6 measures of SBP and DBP were available for ALSPAC participants from research clinics held when the participants were approximately 7, 9, 10, 11, 13, 15 and 17 years old. For each participant we took a measure of BP from any clinic relevant to each epoch to maximise participation and sample size. For example, for the pre-pubertal epoch we predominantly used the 7 year clinic results, but for any child with no measurement at that clinic but who had a BP measure at the 9 year follow-up that was taken when they were less than 8 years we used that. This resulted in measures of SBP and DBP that were contributed to the following epochs: pre-pubertal (N = 3019, mean age 7.5 years), pubertal (N = 3130, mean age = 9.8 years) and post-pubertal (N = 2345, mean age = 15.4 years).

Within ALSPAC, participants were genotyped using the Illumina HumanHap550 quad genome-wide SNP genotyping platform by 23andMe subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, US. Participants were excluded on the basis of having incorrect sex assignments; minimal or excessive heterozygosity (<0.32 and >0.345 for the Sanger data and <0.31 and >0.33 for the LabCorp data); disproportionate levels of individual missingness (>3%); evidence of cryptic relatedness (>10% IBD) and being of non-European ancestry (EIGENSTRAT analysis revealed no additional obvious population stratification and genome-wide analyses with other phenotypes indicate a low lambda). The resulting dataset consisted of 8,365 individuals. SNPs with a minor allele frequency of <1% and call rate of <95% were removed. Furthermore, only SNPs which passed an exact test of Hardy-Weinberg equilibrium ($P>5x10^{-7}$) were considered for analysis. Genotypes were subsequently imputed with MACH 1.0.16 Markov Chain Haplotyping software; using CEPH individuals from phase 2 of the HapMap project as a reference set (release 22).

Lisa Plus

*Influence of **l**ife-style factors on the development of the **i**mmune **s**ystem and **a**llergies in East and West Germany **Plus** the influence of traffic emissions and genetics, Neuherberg, Germany*

The LISAplus study is an ongoing population-based birth cohort study of infants designed to assess "Influences of Lifestyle related Factors on the Immune System and the Development of Allergies in Childhood." The design and objective of this prospective birth cohort study have been described in detail elsewhere [10, 11]. In brief, 3097 newborns were recruited between November 1997 and January 1999 from 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef. The study was conducted with appropriate institutional ethics approval, and written informed consent was obtained from parents at follow-ups. Further details about this study can be found at the study website http://www.helmholtz-muenchen.de/en/epi1/research/.

SBP and DBP was measured twice (the second measurement was used) in a sitting position from the right arm after five minutes of rest during the clinical examination at the study centre. BP measured on the right arm, except in the case of injuries or other obstacles (e.g., gypsum) when it was measured on the left arm. The measurement was performed with the child in a sitting position after 5 min rest. The elbow was relaxed, at heart level, and slightly bent, and the upper arm was bare during testing. A second measurement was taken after sitting for a further 2 min. An automatic blood pressure monitor (Omron M5 Professional) was used for the blood pressure measurements. The cuff size was selected according to the length and circumference of the upper arm of each child: the width was at least 2/3 the length and the pressure bladder covered at least half of the circumference of the upper arm. The average of the two measurements was used throughout this analysis, regardless of the difference between the two records (we excluded 11 subjects who had only one measurement).

DNA was collected at the age 6 and 10 years from the Munich subgroup using standardised procedures and analysed using the Affymetrix Human SNP Array 5.0 for each individual. Genome-wide genotypes were called using BRLMM-P algorithm and imputed in IMPUTE[12] against Hapmap phase2 build 36 release 22 after quality control (MAF>1%, HWE>$1x10^{-2}$, call rate per SNP and person >95%).

Blood pressure was transformed to z-scores and genome-wide association analysis was conducted using SNPTEST assuming an additive genetic effect. This cohort contributed to the pubertal epoch (N = 282, mean age = 10.2 years).

YFS

*The Cardiovascular Risk in **Y**oung **F**inns **S**tudy, Turku, Finland*

Cardiovascular Risk in Young Finns (YFS) is an ongoing collaborative study between five Finnish university medical schools (Helsinki, Turku, Oulu, Kuopio, and Tampere) of risk factors for atherosclerosis. Between 1980 and 1992, 3596 subjects were followed up at 3-year intervals, and then as adults in 2001 and 2007 [13]. Informed consent was collected from all study participants. The study design was approved by the local ethics committee. Further details about this study can be found at the study website http://youngfinnsstudy.utu.fi/.

BP was measured by using a standard mercury sphygmomanometer at baseline and a random zero sphygmomanometer (Hawksley&Sons Ltd, Lancin, UK) at follow-up. All measurements were taken on the right arm, before venipuncture (among adults after venipuncture), and after the participant had been seated for 5 minutes. Readings to the nearest even number of millimeters of mercury were performed at least 3 times on each participant. The mean of these 3 measurements was used in the analyses.

High throughput genome-wide SNP genotyping using the genome-wide Illumina 670K SNP chip at the Wellcome Trust Sanger Centre was performed for each individual. Genotype data were imputed against Hapmap phase2 build 36 release 22 using MACH after quality control (MAF>1%, HWE>$1x10^{-6}$, call rate per SNP and person >95%). Genome-wide association analysis of the SBP and DBP phenotype was carried out in ProAbel. This cohort contributed to the pre-pubertal epoch (N = 400, mean age = 6 years) and the pubertal epoch (N = 842, mean age = 10.5 years).

INMA

*Spanish INMA—**IN**fancia y **M**edio **A**mbiente, Barcelona, Catalonia, Spain*

The INMA Project is a prospective population-based birth cohort study examining associations between pre- and post-natal environmental exposures and growth, health and development of children from early life through adolescence [14]. Between November 2003 and February 2008 a total of 2150 women who fulfilled the inclusion criteria were recruited during the first pre-natal visit. The study was approved by the Ethical Committees of the centres involved in the study and participants provided written informed consent. Further details about this study can be found at the study website http://proyectoinma.org/en_index.html.

During the 4.5 years follow-up visit, blood pressure was measured on children in a sitting position after a 5 minute child rest. Two or three measurements were taken at intervals of 2 min with an OMRON M4-I monitor (digital readings) using the appropriate cuff size. The first blood pressure measure was discarded and the average of the remaining measures or the second measurement when a third measurement was not taken was converted to a Z-score for analyses.

DNA was obtained from cord blood using the Chemagen protocol at the Spanish National Genotyping Centre (CEGEN) Barcelona-node. Children whose parents reported to be white and to be born in Spain or in European countries were selected for genotyping. Genome-wide genotyping was performed using the HumanOmni1-Quad Beadchip (Illumina) at CEGEN. Genotype calling was done with the GeneTrain2.0 algorithm based on HapMap clusters implemented in the Genome Studio software. We applied the following initial quality control thresholds: sample call rate>98% and/or LRR SD<0.3 (excluded: N=4 from INMA-Valencia). PLINK was used for the genetic data quality control. We checked sex, relatedness, heterozygosity and population stratification. All subjects grouped in one cluster. Genetic variants were filtered for SNP call rate>95%, MAF>1% and HWE p value>$1x10^{-6}$, prior to imputation with IMPUTE v.2 using HapMap CEU rel 22. Imputed data was not filtered by imputation quality. Analyses were performed with the SNPtest program. This cohort contributed to the pre-pubertal epoch (N = 600, mean age = 4.3 years).

BLTS

Brisbane Longitudinal Twin Study*, Brisbane, Queensland, Australia*

Twins were initially recruited through the ongoing Queensland Twin Register (1992-2012) where twins were evaluated for melanoma risk factors [15]. Ethics approval for this study was received from the Human Research Ethics Committee of the Queensland Institute of Medical Research. Written informed consent was obtained from each participant and their parent/guardian (if younger than 18 years) prior to testing and participants agreed to donate a blood sample for DNA isolation and genotyping.

At each visit, blood pressure was measured once with the subject sitting, with either a Baumanometer Wall Unit (prior to December 2010) or an Omron HEM-907 Digital Blood Pressure Monitor. Blood pressure measures were converted to a Z-score used in GWAS analyses. Three individuals exceeding four standard deviations from the mean were identified and excluded from analysis.

High throughput genome-wide SNP genotyping using the genome-wide Illumina Human610-Quadv1 Array was performed for each individual. Genotype data were imputed against HapMap phase2 build 36 release 22 using MACH v1.0 after quality control (MAF>1%, HWE>$1x10^{-6}$, call rate per SNP and person >95%). Genome-wide association analysis of the SBP and DBP phenotype was carried out in MERLIN v1.1.2. Prior to the GWAS, 12 ethnic outliers were excluded using Principal components analysis of genome-wide SNP data with Eigenstrat. Zygosity was assessed using nine polymorphic DNA microsatellite markers (AmpF1STR Profiler Plus Amplification Kit, Applied Biosystems, Foster City, CA, USA) and three blood groups (ABO, MNS and Rh), giving a probability of correct assignment >99.99%[16]. This cohort contributed to the pubertal epoch (N = 298, mean age = 12.1 years) and post-pubertal epoch (N = 117, mean age = 16.0 years).

Comparative adult blood pressure GWAS Consortium

ICBP

International **C**onsortium of **B**lood **P**ressure

Most of the studies contributing to the ICBP-GWAS were general population samples, and were recruited for classical or genetic epidemiological purposes. All participants provided written informed consent and studies were approved by their local Research Ethics Committees and/or Institutional Review Boards. Blood pressure, height, and weight were directly measured in all participants. Sex and age were also recorded for all individuals.

All studies with GWAS data performed genotyping using commercially available arrays with >300,000 SNPs. Each study undertook quality-control procedures and excluded individual problematic samples and SNPs, using criteria such as excessive rates of genotyping error, a large proportion of missing genotypes, or marked deviations from Hardy-Weinberg equilibrium. All studies with GWAS data used hidden Markov model approaches[17, 18] and HapMap reference panels[19] to impute genotypes at unmeasured SNPs and excluded SNPs, so that a common set of ~2.5M HapMap SNPs were available across the discovery samples[20].

Supplementary Tables

Study	Raine	GenerationR	ALSPAC	Lisa Plus	YFS	INMA	BLTS
GENOTYPING							
Array type/ Genotyping platform & SNP panel	Illumina Human660W Quad Array	Illumino 610k Quad array	Illumina HumanHap550	Affymetrix Human SNP Array 5.0	Illumina 670k custom	HumanOmni1-Quad Beadchip (Illumina)	Illumina Human610-Quadv1 Array
In silico/de novo	In silico	In silico	In silico	In silico	In silico	In silico	In silico
Genotyping centre	Centre for Applied Genomics, Toronto	Genetic Laboratory-Dept Internal Medicine - Erasmus MC The Netherlands	WTSI, UK, Laboratory Corporation of America, Burligton, NC, USA	Helmholtz Center Munich	Wellcome Trust Sanger Institute	Spanish National Genotyping Center (CEGEN)	deCODE Genetics, Reykjavik, Iceland
Genotype calling algorithm	Illumina Beadsation Genotyping Solution	Genomestudio 2009 V.1.1.9	Illumina	BRLMM-P	Illuminus	GeneTrain2.0	Illumina GenomeStudio v2.0
SAMPLE QC							
SNP call rate (%)	95	95	95	95	95	98	97
Ethnic outliers excluded	Adjusted for principal components	Based on principal component analysis	HAPMAP scaled MDS & Eigenstrat	Ethnic outliers excluded	Ethnic outliers excluded	Adjusted for principal components	Ethnic outliers excluded

SNP QC (prior to imputation)							
Exclusion of SNPs used for imputation	Call rate > 95% HWE < $5.7x10^{-7}$ MAF > 0.10	Call rate > 95% HWE < $1x10^{-6}$ MAF >0.01	Call rate >95% HWE < $5x10^{-7}$ MAF >0.01	Call rate >95% HWE < 0.01 MAF > 0.01	Call rate > 95% HWE > $1x10^{-6}$ MAF > 0.01	Call rate >98% HWE > $1x10^{-6}$ MAF > 0.01	Call rate ≥ 95% HWE < $1x10^{-6}$ MAF ≥ 0.10
HWE threshold	< 1 x 10^{-6}	< 1 x 10^{-6}	<5 x 10^{-7}	> 0.01	< 1 x 10^{-6}	< 1 x 10^{-6}	< 1 x 10^{-6}
Imputation Software	MACH	MACH	MACH	IMPUTE	MACH	IMPUTE v2	MACH 1.0
Analysis Software	MACH2DAT	MACH2QTL implemented on GRIMP	MACH2QTL	SNPTEST	ProbAbel	SNPTEST	MERLIN-OFFLINE
Imputation Backbone (NCBI build)	Hapmap CEU release 22 build 36	Hapmap CEU release 22 build 36	Hapmap CEU release 22 build 36	Hapmap CEU release 22 build 36	HapMap 2 CEU, release 22, build 36	Hapmap CEU release 22 build 36	Hapmap CEU release 22 build 36
Filtering of imputed genotypes	None	None	None	None	None	None	MAF ≥ 0.1, r2 hat ≥ 0.3
Data handling and statistical tests	PLINK and R	MACH2QTL implemented on GRIMP	Stata/Unix/MACH2QTL	R	SAS, R	PLINK and R	MERLIN 1.1.2

Supplementary Table 1: Technical Details of Genotyping, SNP Exclusion, and SNP Imputation Methods by study.

Raine; The Western Australian Pregnancy (**Raine**) Cohort, Perth, Western Australia. **GenerationR;** The **Generation R** Study Group, Rotterdam, The Netherlands**. ALSPAC;** The **A**von **L**ongitudinal **S**tudy of **P**arents and **C**hildren Bristol, UK**. Lisa Plus;** Influence of **l**ife-style factors on the development of the **i**mmune **s**ystem and **a**llergies in East and West Germany **Plus** the influence of traffic emissions and genetics, Neuherberg, Germany. **YFS;** The Cardiovascular Risk in **Y**oung **F**inns **S**tudy, Turku, Finland **. INMA;** Spanish INMA—**IN**fancia y **M**edio **A**mbiente, Barcelona, Catalonia, Spain. **BLTS; Brisbane Longitudinal Twin Study**, **SNP**; Single nucleotide polymorphism; **HWE**; Hardy-Weinberg equilibrium; **MAF**; Minor allele frequency.

Study	Year(s) of birth	Epoch	Subset	Age (years) Mean [range]	SBP (mm Hg) Mean (SD)	DBP (mm Hg) Mean (SD)	Weight (kg) Mean (SD)	Height (m) Mean (SD)	BMI (kg/m^2) Mean (SD)
Raine	1989-1991	Pre-puberty	Sex-combined	5.93 [5.14 - 6.76]	103.18 (8.86)	54.50 (7.32)	21.49 (3.37)	1.16 (0.05)	15.86 (1.75)
			Males	5.92 [5.14 - 6.76]	102.98 (8.59)	54.14 (7.33)	21.76 (3.42)	1.17 (0.05)	15.88 (1.68)
			Females	5.93 [5.53 - 6.03]	103.37 (9.13)	54.88 (7.30)	21.20 (3.30)	1.15 (0.04)	15.84 (1.82)
		Puberty	Sex-combined	10.60 [9.42 - 12.38]	106.98 (9.91)	56.59 (6.74)	39.04 (9.04)	1.44 (0.07)	18.70 (3.41)
			Males	10.60 [10.00 - 12.38]	107.13 (10.05)	56.52 (6.90)	38.86 (9.09)	1.44 (0.07)	18.60 (3.37)
			Females	10.59 [9.42 - 11.66]	106.81 (9.75)	56.68 (6.57)	39.25 (8.98)	1.44 (0.06)	18.81 (3.46)
		Post-puberty	Sex-combined	17.05 [16.02 - 18.33]	115.03 (10.75)	59.46 (6.41)	69.05 (14.94)	1.73 (0.09)	23.13 (4.44)
			Males	17.01 [16.02 - 18.25]	119.79 (10.05)	59.15 (6.44)	73.73 (15.30)	1.79 (0.07)	22.97 (4.41)
			Females	17.03 [16.60 - 18.33]	110.16 (9.16)	59.79 (6.37)	64.18 (12.88)	1.66 (0.06)	23.29 (4.47)
GenerationR	2002-2006	Pre-puberty	Sex-combined	6.09 [4.89 - 8.62]	102.34 (8.05)	60.32 (6.83)	22.72 (3.27)	1.19 (0.05)	15.87 (1.38)
			Males	6.09 [4.89 - 8.62]	101.64 (7.75)	59.74 (6.91)	22.86 (3.15)	1.20 (0.05)	15.87 (1.31)
			Females	6.09 [4.97 - 8.22]	103.06 (8.29)	60.91 (6.70)	22.56 (3.39)	1.19 (0.06)	15.86 (1.45)
ALSPAC	1991-1992	Pre-puberty	Sex-combined	7.50 [6.80 - 9.38]	97.74 (9.51)	55.50 (7.361)	25.86 (4.60)	1.26 (0.06)	16.23 (2.04)
			Males	7.50 [6.80 - 9.38]	97.71 (9.44)	55.07 (7.39)	25.85 (4.41)	1.26 (0.06)	16.11 (1.89)
			Females	7.50 [6.97 - 9.38]	97.76 (9.58)	55.95 (7.30)	25.87 (4.78)	1.25 (0.06)	16.34 (2.16)
		Puberty	Sex-combined	9.83 [8.72 - 11.62]	101.71 (9.55)	56.72 (6.85)	34.66 (7.32)	1.40 (0.06)	17.67 (2.82)
			Males	9.83 [8.72 - 11.54]	101.49 (9.34)	56.40 (6.90)	34.41 (7.05)	1.40 (0.06)	17.48 (2.71)
			Females	9.83 [8.80 - 11.62]	101.93 (9.75)	57.03 (6.80)	34.90 (7.58)	1.39 (0.06)	17.87 (2.92)
		Post-puberty	Sex-combined	15.38 [14.19 - 17.35]	122.28 (11.38)	67.06 (9.81)	61.47 (11.74)	1.69 (0.08)	21.39 (3.50)
			Males	15.30 [14.44 - 17.26]	125.02 (10.64)	67.71 (10.31)	64.15 (12.30)	1.74 (0.08)	21.01 (3.37)
			Females	15.40 [14.19 - 17.35]	119.79 (11.45)	66.46 (9.29)	59.04 (10.63)	1.65 (0.06)	21.74 (3.58)

Lisa Plus	1998-1999	Puberty	Sex-combined	10.19 [9.84 - 10.91]	107.96 (8.61)	63.36 (7.25)	35.05 (6.89)	1.43 (0.06)	17.00 (2.51)
			Males	10.18 [9.84 - 10.91]	108.16 (8.76)	62.16 (6.88)	35.48 (7.11)	1.44 (0.06)	17.10 (2.66)
			Females	10.20 [9.95 - 10.81]	107.68 (8.43)	62.64 (7.75)	34.49 (6.57)	1.42 (0.07)	16.84 (2.28)
YFS	1968-1974	Pre-puberty	Sex-combined	6.00 [6.00 - 6.00]	106.18 (8.29)	65.49 (8.68)	22.54 (3.81)	1.20 (0.06)	15.59 (1.76)
			Males	6.00 [6.00 - 6.00]	106.26 (7.36)	65.11 (8.33)	23.11 (3.98)	1.21 (0.06)	15.66 (1.76)
			Females	6.00 [6.00 - 6.00]	106.12 (8.93)	65.78 (8.93)	22.13 (3.64)	1.19 (0.05)	15.54 (1.75)
		Puberty	Sex-combined	10.51 [9.00 - 12.00]	111.61 (9.38)	68.63 (9.35)	37.00 (9.69)	1.45 (0.11)	17.37 (2.55)
			Males	10.45 [9.00 - 12.00]	111.08 (9.00)	69.13 (9.55)	36.38 (9.11)	1.44 (0.11)	17.26 (2.34)
			Females	10.56 [9.00 - 12.00]	112.07 (9.68)	68.20 (9.17)	37.53 (10.15)	1.45 (0.11)	17.47 (2.72)
INMA	2004-2006	Pre-puberty	Sex-combined	4.30 [3.98 - 4.94]	98.40 (12.16)	61.77 (14.17)	17.99 (2.55)	1.05 (0.04)	16.28 (1.69)
			Males	4.31 [4.01 - 4.94]	98.84 (12.27)	60.79 (12.84)	18.20 (2.65)	1.06 (0.04)	16.23 (1.70)
			Females	4.29 [3.98 - 4.82]	97.90 (12.07)	62.90 (15.56)	17.76 (2.42)	1.04 (0.04)	16.34 (1.68)
ATR	1985-1995	Puberty	Sex-combined	12.15 [12.01 - 12.95]	108.23 (9.91)	64.93 (7.89)	44.79 (10.11)	1.52 (0.08)	19.21 (3.34)
			Males	12.14 [12.01 - 12.95]	108.00 (10.68)	64.90 (8.62)	44.75 (10.40)	1.51 (0.07)	19.42 (3.54)
			Females	12.15 [12.01 - 12.95]	108.45 (9.14)	64.97 (7.13)	44.83 (9.84)	1.53 (0.08)	19.01 (3.14)
		Post-puberty	Sex-combined	16.04 [13.61 - 21.29]	112.85 (10.81)	68.93 (7.61)	62.37 (13.94)	1.68 (0.10)	21.86 (3.87)
			Males	15.99 [14.01 - 21.29]	115.59 (10.77)	69.67 (7.86)	66.47 (14.81)	1.73 (0.09)	22.05 (4.01)
			Females	16.08 [13.61 - 20.79]	110.18 (10.18)	68.20 (7.29)	58.38 (11.76)	1.64 (0.07)	21.67 (3.72)

Supplementary Table 2: Averages for age, SBP and DBP across cohort, sex and epoch

Raine; The Western Australian Pregnancy (**Raine**) Cohort, Perth, Western Australia. **GenerationR;** The **Generation R** Study Group, Rotterdam, The Netherlands**. ALSPAC;** The **A**von **L**ongitudinal **S**tudy of **P**arents and **C**hildren Bristol, UK**. Lisa Plus;** Influence of **l**ife-style factors on the development of the **i**mmune **s**ystem and **a**llergies in East and West Germany **Plus** the influence of traffic emissions and genetics, Neuherberg, Germany. **YFS;** The Cardiovascular Risk in **Y**oung **F**inns **S**tudy, Turku, Finland **. INMA;** Spanish INMA—**IN**fancia y **M**edio **A**mbiente, Barcelona, Catalonia, Spain. **BLTS; Brisbane Longitudinal Twin Study**, Brisbane, Queensland, Australia.

Systolic Blood Pressure (EAGLE Meta-Analysis)				
Marker Name (CHR.POS)	Gene	Related to human BP	Animal model with BP or vascular phenotype or regional linkage to BP?	Relationship of gene, region, SNP or gene product with another disease [GeneCards]
rs1563894 (15. 66422829)	ITGA11		Hypertrophic cardiomyopathy (HCM)[21] and coronary artery disease[22].	Include tick infestation, and hypertrophic cardiomyopathy.
rs3735398 (7.36412646)	ANLN		Associated with carotid intimal-media thickness[23], a predictor of atherosclerosis.	Lower lip cancer, and lip cancer
rs3787159 (20.56252573)	PPPR41L			
rs872256 (9.2496480)	Near SMARCA2, VLDLR.		SWI/SNF complexes are particularly important in cardiovascular tissues (mice studies)[24]. SMARCA2 is a member of the SWI/SNF family of proteins and is highly similar to the brahma protein, where it has been hypothesized that cardiac hypertrophy and the fetal gene expression program are associated with distinguishable binding of Brm and SMARCA4 on genes[25]. BRM expression is restricted to mesodermal tissues involved in early vasculogenesis and heart morphogenesis (mice studies)[26] Significant upregulations of VLDLR were observed in the overweight condition and their expression levels are likely to be closely linked to the phenotypic biomarkers for obesity (mice studies)[27, 28] VLDLR-induced lipid accumulation in the ischemic heart worsens survival by increasing ER stress and apoptosis (mice studies)[29]. VLDLR associated with lipid (LDLD-C) from GWAS in human studies[30]. Ingenuity pathway analyses showed found plausible biological links between Vascular endothelial growth factor (VEGF – known to affect angiogenesis, atherosclerosis, and cancer) with VLDLR from human GWAS analyses[31].	Diseases associated with SMARCA2 include Nicolaides Baraitser syndrome, and smarca2-related Coffin-Siris syndrome. Diseases associated with VLDLR include dysequilibrium syndrome, and cerebellar hypoplasia.
rs9667878 (11.5180326)	OR51V1			Thalassemia, and neuronitis

rs1010366 (7.7196351)	C1GALT1		Postnatal inactivation of C1GALT1 caused blood/lymphatic vessel misconnections that were similar to the vascular defects in the EHC T-syn$^{-/-}$ mice[32]. EHC T-syn$^{-/-}$ mice = exhibited embryonic and neonatal lethality associated with disorganized and blood-filled lymphatic vessels. Potential interaction between C1GALT1 and susceptibility with IgA nephropathy in Chinese populations[33, 34] and Europeans[35].	Iga glomerulonephritis, and glomerulonephritis
rs4538187 (2.63957245)	UGP2			Bilirubin metabolic disorder, and galactosemia
rs3901287 (8.23240509)	LOXL2		LOX/LOXL (includes LOXL1-LOXL4 proteins) shown to be important to the stability of the vessel wall from studies in mice with development of abdominal aortic aneurysms[36]. LOXL2 shown to be associated with vascular elastogenesis[37]	Wilson disease, and malignant peripheral nerve sheath tumor

Supplementary Table 3: Summary known BP (and BP-related effects) for significant genes and variants associated with SBP in sex-combined meta-analysis across EAGLE (all epochs).

Diastolic Blood Pressure (EAGLE Meta-Analysis)				
Marker Name (CHR.POS)	Gene	Related to human BP	Animal model with BP or vascular phenotype or regional linkage to BP?	Relationship of gene, region, SNP or gene product with another disease [GeneCards]
rs241264 (1.4518898)	Between LOC284661 and AJAP1			Diseases associated with AJAP1 include choroid plexus papilloma, and dental caries.
rs1714524 (3.159755790)	LOC100996447			
rs13040824 (20.2225869)	C1GALT1		Postnatal inactivation of C1GALT1 caused blood/lymphatic vessel misconnections that were similar to the vascular defects in the EHC T-syn$^{-/-}$ mice[32] (EHC T-syn$^{-/-}$ mice = exhibited embryonic and neonatal lethality associated with disorganized and blood-filled lymphatic vessels)[32]. Potential interaction between C1GALT1 and susceptibility with IgA nephropathy in Chinese populations[33, 34] and Europeans[35].	Iga glomerulonephritis, and glomerulonephritis
rs1499581 (1.206701240)				
rs16875222 (8.107955966)	Near ABRA (also known as STARS), OXR1		ABRA (or STARS) deficiency severely disrupts cardiac development and function *in vivo* and revealed a novel STARS-SRF feed-forward auto-regulatory loop that could play an essential role in (ABRA) STARS regulation and cardiac functi on (zebrafish model)[38]. Implicated in cardiac development and postnatal cardiac function/homeostasis[39]. Repression of ABRA (STARS) within embryonic, neonatal, and adult hearts via gene GATA4 has shown major implications for MRTF-SRF signaling in the context of cardiac development and disease (mice studies)[39]. Fluid sheer stress-induced ABRA expression during arteriogenesis is triggered by NO and leads to stimulation of collateral growth by smooth muscle cell proliferation[40].	Diseases associated with ABRA include granulomatous angiitis, and retinal drusen. Diseases associated with OXR1 include neuroblastoma, and breast cancer.
rs12237240 (9.28329306)	LINGO2			Neuronitis, and essential tremor
rs1387977 (12.71307607)	TRHDE			Good syndrome, and adenohypophysitis

rs6949619 (7.24396900)	Near NPY	Showed evidence of linkage with any phenotype in the supine position (posture), which is thought to contribute to BP variability[41].	Has a vast range of effects in the cardiovascular, immune, and central and peripheral nervous systems[42]. NPY exerts marked portal hypotensive effects and ameliorates the hyperdynamic circulation in cirrhotic ascitic rats[43]. Comparison of profiles of young and adult BPH/2J mice, after adjusting for maturation genes identified NPY as potentially causative mechanisms involved in hypertension etiology and maintenance in the hypothalamus[44].	Reflex sympathetic dystrophy, and neuroepithelioma
rs229038 (21.27127300)	ADAMTS1		In rats, high resolution positional cloning and translational study showing ADAMTS1 as a candidate gene controlling BP[45]. In men not on pravastatin, those homozygous for the 227Pro allele of ADAMTS1 have a nearly 2-fold increased risk of coronary heart disease events compared with non-carriers[46]. The composition of cardiac jelly essential for myocardial morphogenesis is dynamically controlled by ADAMTS1 and its chromatin-based transcriptional regulation[47]. Modifications to this gene expression are associated with markedly changed blood vessel morphology[48]. Variants within the ADAMTS1 gene have been shown to influence the effectiveness of statins in reducing the risk of myocardial infarction[46, 49] and modulate vascular stability following kidney injury[50]	Type 2a von Willebrand disease, and hypertrophic scars

Supplementary Table 4: Summary known BP (and BP-related effects) for significant genes and variants associated with DBP in sex-combined meta-analysis across EAGLE (all epochs).

Systolic Blood Pressure (Comparison between EAGLE and ICBP)				
Marker Name (CHR.POS)	Gene	Related to human BP	Animal model with BP or vascular phenotype or regional linkage to BP?	Relationship of gene, region, SNP or gene product with another disease [GeneCards]
rs4986146 (17.78534809)	B3GNTL1			Prostatitis
rs17810777 (13.69385636)	KLHL1		KLHL is specifically expressed in the fast skeletal and cardiac muscle (zebrafish studies)[51].	Neuronitis
rs8096788 (18.65451861)	DOK6			Beckwith-Wiedemann syndrome, and neuroblastoma
rs38627 (7.76275543)	LOC100505767 (Speedy Protein E3-Like)			
rs4943826 (11.80730697)				
rs332607 (6.124765053)	NKAIN2			Leukemia
rs3824137 (8.1808899)	ARHGEF10		ARHGEF10 gene was significantly associated with stroke in East Asians; Chinese[52] and Japanese[53, 54]	Slowed nerve conduction velocity, ad, and mental retardation
rs11711274 (3.170597773)	MECOM (also known as EVI1, MDS1, MDS1 And EVI1 Complex Locus)		MECOM belongs to a transcriptional regulatory network that controls heart development (formation of heart tube, BLTSio-ventricular canal) in mice[55]	Myelodysplastic syndromes, and Frasier syndrome
rs17033041 (4.156610757)				
rs293927 (3.14907160)	FGD5		FGD5 is a genetic regulator of vascular pruning by activation of endothelial cell-targeted apoptosis (in mice)[56]. In human cells experiments it has been suggested that FGD5 regulates proangiogenic action of vascular endothelial growth factor vascular endothelial cells[57]	Aarskog-Scott syndrome, and Scott syndrome
rs1687304 (3.14929257)				
rs625757 (1.33922472)	CSMD2		Variants in proximity to CSMD2 were associated with sudden cardiac arrest amongst patients with coronary artery disease[58]	Intermediate Charcot-Marie-Tooth neuropathy, and Charcot-Marie-Tooth neuropathy.

Supplementary Table 5: Summary known BP (and BP-related effects) for significant genes and variants associated with SBP in sex-combined meta-analysis from EAGLE (all epochs) and ICBP.

Diastolic Blood Pressure (Comparison between EAGLE and ICBP)				
Marker Name (CHR.POS)	Gene	Related to human BP	Animal model with BP or vascular phenotype or regional linkage to BP?	Relationship of gene, region, SNP or gene product with another disease [GeneCards]
rs6760458 (2.42938973)				
rs7578149 (2.20175919)				
rs11713251 (3.49315011)	USP4			Oculopharyngeal muscular dystrophy, and multiple chemical sensitivity
rs7914808 (10.120991173)	GRK5		GRK5 Leu41 decreased the risk for adverse cardiovascular outcomes[59]. Also shown to be protective in African-American populations[60] Regulation of left cardiac hypertrophy is based on NF-xB transduction signalling being inhibited by GRK5-NT (in rat studies)[61] and vascular smooth muscle (VSM)-specific overexpression of GRK5 elevates BP in both male and female mice[62].	Schizoaffective disorder, and Huntington's disease
rs1951930 (6.33890633)				
rs4650447 (1.80256759)				
rs17064088 (5.174293917)	FLJ16171			

Supplementary Table 6: Summary known BP (and BP-related effects) for significant genes and variants associated with DBP in sex-combined meta-analysis from EAGLE (all epochs) and ICBP.

SNP	CHR: position	Reference allele	Other allele	Reference allele frequency	Log odds	Log odds standard error	p-value	Number of cases	Number of controls
rs1563894	chr15:66422829	G	A	0.241	-0.009	0.022	0.694	11496	49362
rs872256	chr9:2486480	T	A	0.254	0.006	0.016	0.717	19695	60475
rs1010366	chr7:7196351	C	T	0.303	0.014	0.015	0.360	20105	61078
rs13040824	chr20:2173869	G	A	0.772	0.008	0.018	0.634	21234	61923
rs12365302	**chr11:45731573**	**G**	**A**	**0.134**	**-0.054**	**0.021**	**0.008**	**19847**	**60749**
rs3735398	chr7:36412646	G	A	0.126	-0.009	0.022	0.666	19096	60033
rs3787159	**chr20:56252573**	**C**	**T**	**0.461**	**-0.029**	**0.014**	**0.039**	**20171**	**61115**
rs9667878	chr11:5180326	C	T	0.942	0.037	0.031	0.226	20592	61484
rs4538187	chr2:63957245	G	A	0.195	0.013	0.017	0.470	21941	62251
rs3901287	chr8:23240509	T	A	0.761	0.011	0.021	0.621	11314	50640
rs241264	chr1:4518898	C	T	0.181	-0.008	0.019	0.657	20605	61412
rs1714524	chr3:159755790	C	T	0.433	0.013	0.014	0.376	20510	58834
rs16875222	**chr8:107955966**	**T**	**A**	**0.906**	**0.061**	**0.029**	**0.037**	**19986**	**60855**
rs12237240	chr9:28329306	G	T	0.701	-0.029	0.019	0.136	10227	49469
rs1387977	chr12:71307607	G	T	0.937	-0.027	0.029	0.340	20539	61427
rs6949619	chr7:24396900	C	T	0.710	0.006	0.016	0.694	19154	59806
rs229038	chr21:27127300	C	G	0.064	-0.020	0.040	0.625	20354	61260

Supplementary Table 7: Comparison of EAGLE meta-analysis results with CARDIOGRAM. Beta values are in terms of Z-scores, the number of standard deviations away from the mean. Highlighted in bold text are the SNPs reaching $p<0.05$ in CARDIOGRAM.

Systolic Blood Pressure												
Timeframe	Subset	Marker Name	Allele	CHR	POS	MAF	Gene	Beta (95%CI)	*p*	Direction	ICBP *p*	N-effective
Pre-pubertal	Females	rs2339469	A/G	2	29392364	0.37	ALK	-0.102(-0.142,-0.061)	1.13E-06	----+	0.71	5,008
		rs6798160	T/C	3	4832780	0.39	ITPR1	-0.096(-0.137,-0.054)	6.22E-06	-----	NA	5,008
		rs10506710	C/G	12	71736584	0.49		-0.098(-0.139,-0.056)	3.24E-06	-----	0.39	5,008
	Males	rs7179228	T/G	15	66409401	0.30	ITGA11	0.121(0.077,0.166)	1.10E-07	+++++	0.59	5,082
		rs12339966	A/T	9	11631243	0.18		0.134(0.085,0.184)	1.18E-07	+++++	0.38	5,082
Pubertal	Females	rs6946404	C/G	7	89672869	0.03		0.193(0.107,0.279)	1.40E-05	++++-	0.09	4,238
		rs6033063	A/T	20	11160307	0.44		-0.084(-0.121,-0.047)	1.61E-05	---+-	0.98	4,238
		rs7527591	A/G	1	98841095	0.16	Near SNX7	0.093(0.050,0.136)	1.84E-05	+++++	0.25	4,238
		rs1384882	T/C	1	74271874	0.16	LRRIQ3	0.159(0.086,0.232)	1.84E-05	++-++	0.22	4,238
	Males	rs3735398	A/G	7	36412646	0.11	ANLN	0.159(0.100,0.218)	1.42E-07	+++++	0.75	4,185
		rs4974559	A/G	4	1370848	0.43	KIAA1530	-0.117(-0.168,-0.066)	7.21E-06	-----	0.28	4,185
		rs7011049	A/C	8	53996565	0.12		-0.125(-0.180,-0.070)	7.07E-06	-----	0.62	4,185
Post-pubertal	Females	rs996004	A/G	4	44773765	0.03	Near: GUF1, GNPDA2	0.256(0.154,0.358)	9.35E-07	+++	0.12	2,680
		rs11120167	T/G	1	211839047	0.41	Near: RPS6KC1	-0.118(-0.171,-0.065)	1.29E-05	---	0.89	2,680
	Males	rs1905116	T/C	1	223258306	0.24	DNAH14	0.108(0.059,0.157)	1.36E-05	+++	0.53	2,496
		rs13095912	A/G	3	186784792	0.35	SENP2	-0.114(-0.163,-0.065)	7.44E-06	---	0.16	2,496

Supplementary Table 8: Top SNP clusters from Systolic Blood Pressure meta-analyses in EAGLE. P-values from ICBP are listed for reference. Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

Diastolic Blood Pressure												
Timeframe	Subset	Marker Name	Allele	CHR	POS	MAF	Gene	Beta (95% CI)	*p*	Direction	ICBP *p*	N-effective
Pre-pubertal	Females	rs850892	T/C	2	185917555	0.50		0.101(0.06,0.142)	9.98E-07	++++-	0.55	5,008
		rs2820475	A/G	1	68472956	0.04		0.247(0.142,0.352)	4.30E-06	+++++	NA	5,008
	Males	rs305460	A/T	1	87964818	0.20		0.115(0.066,0.164)	4.77E-06	++++-	0.66	5,082
		rs1114504	T/C	11	78915535	0.25	Near: ODZ4	-0.123(-0.178,-0.068)	6.25E-06	----+	0.34	5,082
Pubertal	Females	rs17774123	T/G	12	52527546	0.10		-0.136(-0.191,-0.081)	9.69E-07	-----	NA	4,238
		rs12370001	T/C	12	71330889	0.06	TRHDE	0.204(0.114,0.294)	7.52E-06	+++++	0.80	4,238
	Males	rs12712036	T/C	2	98829143	0.43	KIAA1211L	-0.088(-0.132,-0.044)	7.72E-05	---+-	NA	4,185
		rs1021865	A/G	16	19692192	0.32	IQCK	0.114(0.059,0.170)	5.02E-05	-+++-	0.41	4,185
Post-pubertal	Females	rs12646597	T/C	4	167169368	0.44	TLL1	-0.117(-0.170,-0.064)	1.68E-05	--+	0.30	2,680
		rs10757157	A/G	9	20911025	0.38	KIAA1797	0.110(0.057,0.163)	5.23E-05	++-	0.70	2,680
		rs9968204	C/G	3	25938544	0.08		0.218(0.116,0.320)	2.59E-05	+++	0.20	2,680
	Males	rs10822407	T/C	10	66454106	0.30		-0.149(-0.206,-0.092)	2.07E-07	---	0.25	2,496
		rs2119480	T/C	13	110141889	0.49	CARS2	-0.131(-0.186,-0.076)	2.41E-06	---	0.53	2,496
		rs1146942	A/G	13	79717730	0.31		0.136(0.077,0.195)	4.95E-06	+++	0.68	2,496
		rs17192454	A/G	8	13213767	0.04	DLC1	0.261(0.145,0.377)	1.11E-05	+++	0.73	2,496
		rs9354187	T/C	6	65657839	0.17	EYS	0.231(0.127,0.335)	1.42E-05	+++	0.03	2,496

Supplementary Table 9: Top SNP clusters from Diastolic Blood Pressure meta-analyses in EAGLE. P-values from ICBP are listed for reference. Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

Systolic Blood Pressure									
							ICBP	EAGLE	
Timeframe	Subset	Marker Name	CHR	POS	MAF	Gene	*p*	Beta (95%CI)	*p*
		rs7928369	11	124600431	0.16	PKNOX2	6.73E-04	0.076(0.033,0.119)	4.83E-04
		rs767312	12	27487246	0.35		6.84E-04	0.079(0.036,0.122)	2.80E-04
		rs183777	20	57244560	0.33	ZNF831	7.30E-04	0.066(0.027,0.105)	9.97E-04
		rs7942878	11	124609079	0.17	PKNOX2	7.39E-04	0.077(0.032,0.122)	6.36E-04
	Females	rs9358742	6	24143021	0.45		7.95E-04	-0.064(-0.101,-0.027)	9.17E-04
		rs10502471	18	22360961	0.05	KCTD1	2.73E-03	-0.239(-0.349,-0.129)	2.33E-05
Pre-pubertal	Males	rs7207549	17	40715911	0.17	MAP3K14	4.63E-03	0.070(0.029,0.111)	9.45E-04
		rs11671659	19	17228092	0.01	USHBP1	8.88E-05	0.233(0.104,0.362)	4.47E-04
	Females	rs12417023	11	11565498	0.12	GALNTL4	1.28E-03	0.084(0.035,0.133)	9.17E-04
		rs6989152	8	84876961	0.02		1.34E-03	-0.365(-0.577,-0.153)	7.57E-04
		rs10740411	10	53460631	0.35	PRKG1	2.10E-03	-0.076(-0.121,-0.031)	9.34E-04
Pubertal	Males	rs332607	6	124765053	0.25	NKAIN2	3.19E-03	0.084(0.043,0.125)	6.55E-05
		rs12475465	2	18191492	0.05		9.72E-04	0.185(0.075,0.295)	9.02E-04
		rs4705530	5	112362756	0.23	DCP2	2.59E-03	-0.095(-0.150,-0.040)	6.85E-04
	Females	rs162064	3	109306751	0.27		4.89E-03	0.093(0.042,0.144)	3.90E-04
		rs10994438	10	62059162	0.31	ANK3	3.86E-04	0.082(0.033,0.131)	9.62E-04
		rs625757	1	33922472	0.07	CSMD2	5.43E-04	-0.162(-0.244,-0.080)	1.03E-04
Post-pubertal	Males	rs2480244	1	33925781	0.07	CSMD2	6.13E-04	-0.164(-0.246,-0.082)	8.61E-05

Supplementary Table 10: Comparing SBP meta-analyses in EAGLE and ICBP. Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

Diastolic Blood Pressure									
							ICBP	EAGLE	
	Subset	Marker Name	CHR	POS	MAF	Gene	*p*	Beta (95%CI)	*p*
		rs12473885	2	230277834	0.15	DNER	3.63E-04	-0.113(-0.176,-0.05)	3.53E-04
		rs17820659	12	13580175	0.1		1.03E-03	-0.131(-0.2,-0.062)	1.53E-04
Timeframe	Males	rs11847932	14	102255188	0.26	RCOR1	1.05E-03	0.094(0.041,0.147)	4.61E-04
		rs6687	2	230340512	0.15	TRIP12	3.93E-04	-0.187(-0.289,-0.085)	3.20E-04
		rs11229833	11	58653760	0.44		2.12E-03	0.128(0.061,0.195)	2.00E-04
	Females	rs6502882	17	5642773	0.43		4.58E-03	0.127(0.056,0.198)	4.75E-04
		rs1595373	11	16223316	0.24	SOX6	1.31E-05	0.092(0.039,0.145)	7.27E-04
		rs10786736	10	104839106	0.15	NT5C2	3.83E-05	0.123(0.052,0.194)	7.64E-04
		rs6882088	5	173226782	0.17		5.58E-04	0.079(0.034,0.124)	6.57E-04
Pubertal	Males	rs9900677	17	28944267	0.23	ACCN1	7.15E-04	0.094(0.039,0.149)	9.23E-04
		rs1564823	5	173315800	0.16	CPEB4	1.17E-04	0.09(0.037,0.143)	7.25E-04
		rs2898883	17	44837952	0.2	PHB	1.23E-03	-0.087(-0.138,-0.036)	9.59E-04
	Females	rs12664699	6	127249944	0.48		1.30E-03	0.084(0.035,0.133)	6.51E-04
		rs944452	14	52554313	0.19		7.23E-04	-0.122(-0.195,-0.049)	9.24E-04
		rs2269426	6	32184477	0.34	TNXB	1.36E-03	-0.093(-0.148,-0.038)	9.69E-04
Post-pubertal	Males	rs10151030	14	52576159	0.22	DDHD1	1.60E-03	-0.12(-0.193,-0.047)	9.80E-04

Supplementary Table 11: Comparing DBP meta-analyses in EAGLE and ICBP. Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

Pre-pubertal	**Sex: SNP interaction**		**Combined**	**Stratified**	
SNP	Beta (95%)	p	p	Sex	p
rs1563894	0.046(-0.078, 0.169)	0.472	2.86E-08*	Males	4.51E-07
Pubertal	**Sex: SNP interaction**		**Combined**	**Stratified**	
SNP	Beta (95%)	p	p	Sex	p
rs3735398	-0.019(-0.069, 0.029)	0.429	8.76E-06	Males	1.42E-07
rs9667878	-0.001(-0.129, 0.127)	0.991	9.74E-06	Females	5.78E-06
DBP					
Pre-pubertal	**Sex: SNP interaction**		**Combined**	**Stratified**	
SNP	Beta (95%)	p	p	Sex	p
rs11679280	-0.214(-1.601, 1.173)	0.763	6.50E-03	Males	4.66E-09*
Pubertal	**Sex: SNP interaction**		**Combined**	**Stratified**	
SNP	Beta (95%)	p	p	Sex	p
rs7897969	-0.015(-0.188, 0.158)	0.867	4.82E-07	Males	5.78E-10*

Supplementary Table 12: Comparing significant SNPs from sex-stratified meta-analyses to single cohort analyses with sex by SNP interactions

Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

SBP											
Marker Name	CHR	POS	Gene	MAF	Allele	Pre-Pubertal			Pubertal		
						Beta (95% CI)	P-value	Direction	Beta (95% CI)	P-value	Direction
rs13025174	2	46557999		0.56	A/G	0.075(0.031,0.12)	9.37E-04	++++	0.054(0.026,0.082)	1.38E-04	++-++
rs13032473	2	46559169	TMEM247	0.56	A/G	0.076(0.031,0.121)	8.60E-04	++++	0.054(0.026,0.082)	1.38E-04	++-++
rs13033917	2	46559519	TMEM247	0.53	A/G	-0.076(-0.121,-0.031)	8.55E-04	----	-0.054(-0.082,-0.026)	1.38E-04	--+--
rs4953385	2	46559972	TMEM247	0.45	T/G	-0.076(-0.121,-0.032)	8.01E-04	----	-0.054(-0.082,-0.026)	1.38E-04	--+--
rs3814047	2	46560122	TMEM247	0.55	C/G	0.076(0.031,0.121)	8.47E-04	++++	0.054(0.026,0.082)	1.55E-04	++-++
rs2121697	2	46563111	TMEM247	0.56	A/C	0.076(0.031,0.12)	9.09E-04	++++	0.053(0.025,0.081)	2.03E-04	++-++
rs2300438	2	49060571	FSHR	0.87	T/C	0.119(0.052,0.185)	4.57E-04	++++	0.07(0.029,0.111)	8.36E-04	++--+
rs6753729	2	49062087	FSHR	0.87	C/G	0.119(0.053,0.186)	4.27E-04	++++	0.07(0.029,0.111)	8.43E-04	++--+
rs1007541	2	49062538	FSHR	0.82	T/C	0.12(0.053,0.186)	3.99E-04	++++	0.07(0.029,0.111)	8.25E-04	++--+
rs13396575	2	49065417	FSHR	0.87	C/G	0.12(0.054,0.186)	3.96E-04	++++	0.07(0.029,0.111)	8.26E-04	++--+
rs10186089	2	49072628	FSHR	0.83	A/G	0.123(0.056,0.19)	3.07E-04	++++	0.073(0.031,0.114)	5.45E-04	++--+
rs10190280	2	49074394	FSHR	0.83	C/G	0.124(0.057,0.191)	3.08E-04	++++	0.075(0.034,0.116)	3.69E-04	++--+
rs12473181	2	49075319	FSHR	0.87	T/C	0.124(0.056,0.191)	3.17E-04	++++	0.074(0.033,0.115)	4.09E-04	++--+
rs7423208	2	49077561	FSHR	0.88	A/G	0.126(0.057,0.195)	3.74E-04	++++	0.073(0.03,0.115)	8.34E-04	++--+
rs11875941	18	38454837	LINC00907	1.00	T/G	-0.8(-1.222,-0.379)	2.00E-04	-?-?	-0.337(-0.536,-0.139)	8.60E-04	+-+--
						Pre-Pubertal			Post-Pubertal		
rs12723804	1	1.94E+08	LOC105371672	0.98	A/G	0.592(0.3,0.884)	7.09E-05	++-+	0.416(0.204,0.628)	1.21E-04	+++
rs12405248	1	1.94E+08	LOC105371672	0.97	A/G	0.579(0.25,0.909)	5.70E-04	-+-+	0.438(0.204,0.673)	2.45E-04	+++
						Pubertal			Post-Pubertal		
rs161554	5	1.43E+08		0.01	T/C	0.23(0.111,0.349)	1.57E-04	++++-	0.299(0.133,0.465)	4.17E-04	?++
rs4626578	8	56078561		0.12	A/T	-0.069(-0.108,-0.029)	6.68E-04	+----	-0.112(-0.166,-0.059)	3.68E-05	?--
rs2247028	8	56138987		0.88	A/T	0.064(0.027,0.102)	7.87E-04	-++++	0.107(0.057,0.156)	3.05E-05	?++
rs2622389	8	56143870		0.12	T/G	-0.066(-0.104,-0.028)	5.95E-04	+----	-0.106(-0.156,-0.056)	3.58E-05	?--
rs995882	8	56152562		0.88	A/G	0.067(0.029,0.104)	5.18E-04	-++++	0.105(0.055,0.155)	4.00E-05	?++
rs2726422	8	56155034		0.88	A/G	0.067(0.029,0.104)	5.20E-04	-++++	0.105(0.055,0.155)	4.00E-05	?++
rs1480770	8	56165854		0.75	C/G	0.061(0.025,0.097)	8.09E-04	-+-+-	0.082(0.033,0.13)	9.40E-04	?++
rs996825	8	56166906		0.24	T/C	-0.06(-0.094,-0.026)	6.37E-04	+-+-+	-0.089(-0.136,-0.043)	1.81E-04	?--
rs1383450	8	56167423		0.87	T/C	0.073(0.033,0.112)	2.85E-04	+++++	0.115(0.063,0.167)	1.47E-05	?++

Supplementary Table 13a: Comparing SBP meta-analyses across epochs in EAGLE. Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

Marker Name	CHR	POS	Gene	MAF	Allele	Pubertal			Post-Pubertal		
						Beta (95% CI)	P-value	Direction	Beta (95% CI)	P-value	Direction
rs1480768	8	56169231		0.25	T/C	-0.06(-0.094,-0.026)	6.44E-04	+-+-+	-0.088(-0.135,-0.042)	2.14E-04	?--
rs1480767	8	56169234		0.82	C/G	0.066(0.028,0.104)	5.92E-04	-+++-	0.1(0.05,0.15)	9.06E-05	?++
rs1564463	8	56170436		0.16	A/G	-0.065(-0.103,-0.028)	6.29E-04	+---+	-0.1(-0.15,-0.05)	9.06E-05	?--
rs6473970	8	56172747		0.74	A/G	0.06(0.026,0.094)	6.45E-04	-+-+-	0.087(0.041,0.134)	2.33E-04	?++
rs9693329	8	56174118		0.90	T/C	0.068(0.029,0.107)	6.29E-04	++-+-	0.097(0.045,0.15)	2.51E-04	?++
rs7004582	8	56174269		0.90	A/T	0.068(0.029,0.107)	6.65E-04	++-+-	0.097(0.045,0.15)	2.51E-04	?++
rs9694358	8	56183720	XKR4	0.89	A/G	0.067(0.029,0.105)	4.93E-04	++++-	0.098(0.046,0.15)	2.22E-04	?++
rs7004356	8	56198058	XKR4	1.00	T/C	0.068(0.03,0.105)	4.71E-04	++++-	0.099(0.047,0.151)	2.07E-04	?++
rs1480774	8	56199584	XKR4	0.16	T/G	-0.063(-0.1,-0.026)	9.77E-04	+-+-+	-0.099(-0.149,-0.049)	1.17E-04	?--
rs12546351	8	56200312	XKR4	0.13	A/G	-0.063(-0.1,-0.026)	9.69E-04	+-+-+	-0.099(-0.149,-0.049)	1.17E-04	?--
rs276978	16	84783954		0.30	T/C	0.073(0.03,0.117)	9.88E-04	-++-+	0.098(0.043,0.153)	5.26E-04	+++
rs2239382	20	9449526	LAMP5	0.25	C/G	-0.069(-0.108,-0.03)	5.62E-04	--+--	-0.083(-0.131,-0.035)	7.33E-04	---
rs2105871	22	28566588		0.90	T/G	-0.086(-0.136,-0.036)	7.83E-04	--++-	-0.113(-0.174,-0.051)	3.33E-04	---
rs6006276	22	28567859		0.10	A/T	0.088(0.038,0.138)	5.68E-04	++--+	0.114(0.053,0.175)	2.73E-04	+++
rs5752974	22	28601630		0.96	A/G	-0.088(-0.137,-0.04)	3.74E-04	--++-	-0.115(-0.175,-0.055)	1.79E-04	---
rs5763568	22	28603164		0.96	T/C	-0.088(-0.137,-0.04)	3.74E-04	--++-	-0.115(-0.175,-0.055)	1.79E-04	---
rs5752979	22	28634334	MTMR3	0.03	A/G	0.088(0.04,0.137)	3.81E-04	++--+	0.115(0.055,0.175)	1.72E-04	+++
rs5763595	22	28635754	MTMR3	0.96	A/G	-0.088(-0.137,-0.04)	3.81E-04	--++-	-0.116(-0.176,-0.056)	1.50E-04	---
rs1544431	22	28638106	MTMR3	0.96	T/C	-0.088(-0.137,-0.04)	3.81E-04	--++-	-0.116(-0.176,-0.056)	1.50E-04	---
rs737938	22	28643252	MTMR3	0.04	A/G	0.088(0.04,0.137)	3.81E-04	++--+	0.116(0.056,0.176)	1.50E-04	+++
rs36593	22	28664356	MTMR3	0.96	C/G	-0.089(-0.138,-0.04)	3.36E-04	--++-	-0.116(-0.176,-0.056)	1.48E-04	---
rs36599	22	28667049	MTMR3	0.96	T/C	-0.089(-0.138,-0.04)	3.36E-04	--++-	-0.116(-0.176,-0.056)	1.45E-04	---
rs36608	22	28672191	MTMR3	0.02	A/G	0.089(0.041,0.138)	3.27E-04	++--+	0.116(0.056,0.176)	1.47E-04	+++
rs39713	22	28673186	MTMR3	0.96	T/C	-0.089(-0.138,-0.04)	3.45E-04	--++-	-0.116(-0.176,-0.056)	1.40E-04	---
rs16988120	22	28679152	MTMR3	0.96	A/C	-0.089(-0.138,-0.041)	3.24E-04	--++-	-0.117(-0.177,-0.057)	1.26E-04	---
rs16988143	22	28704677	MTMR3	0.04	T/C	0.09(0.041,0.138)	3.05E-04	++--+	0.118(0.057,0.179)	1.61E-04	+++
rs16988148	22	28709494	MTMR3	0.04	T/G	0.09(0.041,0.138)	2.98E-04	++--+	0.119(0.058,0.18)	1.41E-04	+++
rs16988149	22	28710217	MTMR3	0.96	A/G	-0.091(-0.139,-0.042)	2.60E-04	--++-	-0.119(-0.181,-0.058)	1.36E-04	---

Supplementary Table 13b: Comparing SBP meta-analyses across epochs in EAGLE. Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

Marker Name	CHR	POS	Gene	MAF	Allele	Pubertal			Post-Pubertal		
						Beta (95% CI)	P-value	Direction	Beta (95% CI)	P-value	Direction
rs7284951	22	28714092	MTMR3	0.04	T/G	0.091(0.041,0.141)	3.48E-04	++--+	0.12(0.059,0.181)	1.24E-04	+++
rs11552852	22	28754377	HORMAD2-AS1,MTMR3	0.98	T/C	-0.093(-0.142,-0.043)	2.68E-04	--++-	-0.123(-0.185,-0.062)	7.87E-05	---
rs16988244	22	28763373	HORMAD2-AS1	0.04	T/G	0.091(0.042,0.14)	2.46E-04	++--+	0.115(0.055,0.175)	1.71E-04	+++
rs7286205	22	28805154	HORMAD2,HORMAD2-AS1	0.96	A/G	-0.09(-0.138,-0.041)	2.99E-04	--++-	-0.112(-0.172,-0.052)	2.42E-04	---
rs16988291	22	28831105	HORMAD2	0.96	T/C	-0.09(-0.138,-0.041)	3.09E-04	--++-	-0.111(-0.171,-0.051)	2.72E-04	---
rs16988303	22	28835646	HORMAD2	0.04	A/C	0.09(0.041,0.138)	3.08E-04	++--+	0.11(0.051,0.17)	3.02E-04	+++
rs16988304	22	28846140	HORMAD2	0.04	T/C	0.09(0.041,0.138)	3.02E-04	++--+	0.11(0.05,0.17)	3.10E-04	+++
rs8141471	22	28848233	HORMAD2	0.96	A/G	-0.09(-0.138,-0.041)	3.02E-04	--++-	-0.11(-0.17,-0.05)	3.10E-04	---
rs6519805	22	28855549	HORMAD2	0.96	T/C	-0.09(-0.138,-0.041)	3.02E-04	--++-	-0.11(-0.17,-0.05)	3.10E-04	---
rs737901	22	28880380	HORMAD2	0.96	T/C	-0.09(-0.139,-0.041)	2.84E-04	--++-	-0.11(-0.17,-0.05)	3.12E-04	---
rs16988333	22	28882813	HORMAD2	0.04	A/G	0.09(0.041,0.139)	2.84E-04	++--+	0.11(0.05,0.17)	3.12E-04	+++
rs5763855	22	28908964	HORMAD2,LOC105372988	0.04	A/G	0.09(0.041,0.138)	3.17E-04	++--+	0.108(0.046,0.169)	5.88E-04	+++
rs5763856	22	28909250	HORMAD2,LOC105372988	0.96	C/G	-0.09(-0.138,-0.041)	3.17E-04	--++-	-0.108(-0.169,-0.046)	5.88E-04	---
rs5763857	22	28909617	HORMAD2,LOC105372988	0.96	A/C	-0.09(-0.139,-0.041)	2.86E-04	--++-	-0.107(-0.168,-0.045)	6.38E-04	---
rs5763858	22	28909722	HORMAD2,LOC105372988	0.96	A/C	-0.09(-0.138,-0.041)	3.15E-04	--++-	-0.107(-0.168,-0.045)	6.38E-04	---
rs4482600	22	28909886	HORMAD2,LOC105372988	0.04	A/T	0.09(0.041,0.138)	3.15E-04	++--+	0.107(0.045,0.168)	6.38E-04	+++
rs4482601	22	28910373	HORMAD2,LOC105372988	0.04	A/G	0.09(0.041,0.138)	3.15E-04	++--+	0.106(0.045,0.168)	6.80E-04	+++
rs5753038	22	28913134	HORMAD2,LOC105372988	0.05	T/G	0.09(0.042,0.139)	2.79E-04	++--+	0.106(0.045,0.168)	6.80E-04	+++

Supplementary Table 13c: Comparing SBP meta-analyses across epochs in EAGLE. Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

Marker Name	CHR	POS	Gene	MAF	Allele	Pubertal			Post-Pubertal		
						Beta (95% CI)	P-value	Direction	Beta (95% CI)	P-value	Direction
rs5753039	22	28913711	HORMAD2,LOC 105372988	0.04	A/T	0.091(0.042,0.139)	2.77E-04	++--+	0.106(0.045,0.167)	6.93E-04	+++
rs4823078	22	28913889	HORMAD2,LOC 105372988	0.95	T/C	-0.091(-0.139,-0.042)	2.75E-04	--++-	-0.106(-0.167,-0.045)	6.93E-04	---
rs5763870	22	28916396	HORMAD2,LOC 105372988	0.04	A/G	0.088(0.039,0.137)	4.01E-04	++--+	0.105(0.044,0.167)	7.64E-04	+++
rs5753042	22	28917972	HORMAD2,LOC 105372988	0.06	A/G	0.088(0.039,0.137)	3.92E-04	++--+	0.105(0.044,0.167)	7.64E-04	+++
Marker Name	CHR	POS	Gene	MAF	Allele	Pubertal			Post-Pubertal		
						Beta (95% CI)	P-value	Direction	Beta (95% CI)	P-value	Direction
rs5763873	22	28918372	HORMAD2,LOC 105372988	0.94	A/G	-0.087(-0.136,-0.038)	4.84E-04	--++-	-0.105(-0.166,-0.043)	8.29E-04	---
rs5763878	22	28921824	HORMAD2,LOC 105372988	0.04	T/C	0.087(0.038,0.136)	4.72E-04	++--+	0.105(0.043,0.166)	8.29E-04	+++
rs2412980	22	28922069	HORMAD2,LOC 105372988	0.96	T/C	-0.087(-0.136,-0.038)	4.75E-04	--++-	-0.104(-0.166,-0.042)	9.24E-04	---

Supplementary Table 13d: Comparing SBP meta-analyses across epochs in EAGLE. Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

DBP											
Marker Name	CHR	POS	Gene	MAF	Allele	Pre-Pubertal			Pubertal		
						Beta (95% CI)	P-value	Direction	Beta (95% CI)	P-value	Direction
rs13004438	2	179421913	CCDC141,LOC105373766	0.17	T/C	0.082(0.034,0.13)	8.31E-04	+++	-0.053(-0.084,-0.022)	8.10E-04	-----
						Pre-Pubertal			Post-pubertal		
rs12542146	8	10485173		0.23	A/G	0.1(0.041,0.159)	9.29E-04	++?	-0.073(-0.115,-0.03)	8.42E-04	---
rs9373002	6	132279972		0.28	A/G	0.101(0.042,0.159)	7.36E-04	++?	0.072(0.029,0.114)	8.95E-04	+++
						Pubertal			Post-pubertal		
rs2944782	2	47750478		0.21	A/G	0.075(0.033,0.117)	4.35E-04	+++++	0.09(0.041,0.14)	3.31E-04	+++
rs2705775	2	47751370		0.81	T/C	-0.073(-0.115,-0.031)	6.44E-04	----+	-0.091(-0.14,-0.042)	3.05E-04	---
rs12532038	7	124281701	POT1	0.39	T/C	-0.059(-0.09,-0.028)	2.06E-04	----+	-0.067(-0.106,-0.028)	8.25E-04	--+
rs734335	14	100648711		0.40	A/G	-0.092(-0.136,-0.047)	5.23E-05	-----	-0.11(-0.165,-0.055)	9.20E-05	---
rs16944225	16	74921864	CNTNAP4	0.16	C/G	0.116(0.068,0.164)	2.08E-06	++++-	0.099(0.04,0.157)	9.17E-04	+++
rs8058722	16	74923332	CNTNAP4	0.84	A/G	-0.116(-0.164,-0.068)	2.14E-06	----+	-0.099(-0.157,-0.04)	9.17E-04	---
rs8044637	16	74923514	CNTNAP4	0.84	A/T	-0.116(-0.164,-0.068)	2.11E-06	----+	-0.099(-0.157,-0.04)	9.17E-04	---
rs8044400	16	74923996	CNTNAP4	0.84	T/C	-0.116(-0.164,-0.068)	2.10E-06	----+	-0.099(-0.157,-0.04)	9.17E-04	---
rs12325022	16	74930130	CNTNAP4	0.85	A/G	-0.116(-0.164,-0.068)	2.55E-06	----+	-0.1(-0.159,-0.042)	7.47E-04	---
rs2195429	16	74943628	CNTNAP4	0.73	A/T	-0.112(-0.16,-0.064)	5.01E-06	-----	-0.101(-0.159,-0.042)	7.08E-04	---
rs4528602	16	74948793	CNTNAP4	0.23	A/G	0.109(0.061,0.157)	8.17E-06	++++-	0.098(0.04,0.156)	9.43E-04	+++
rs11865582	16	74950606	CNTNAP4	0.61	A/G	-0.055(-0.086,-0.025)	4.15E-04	-----	-0.063(-0.099,-0.027)	6.37E-04	--+
rs12924751	16	74958685	CNTNAP4	0.57	A/G	-0.055(-0.086,-0.025)	4.07E-04	-----	-0.063(-0.099,-0.027)	6.65E-04	--+

Supplementary Table 14: Comparing DBP meta-analyses across epochs in EAGLE. Beta values are in terms of Z-scores, the number of standard deviations away from the mean.

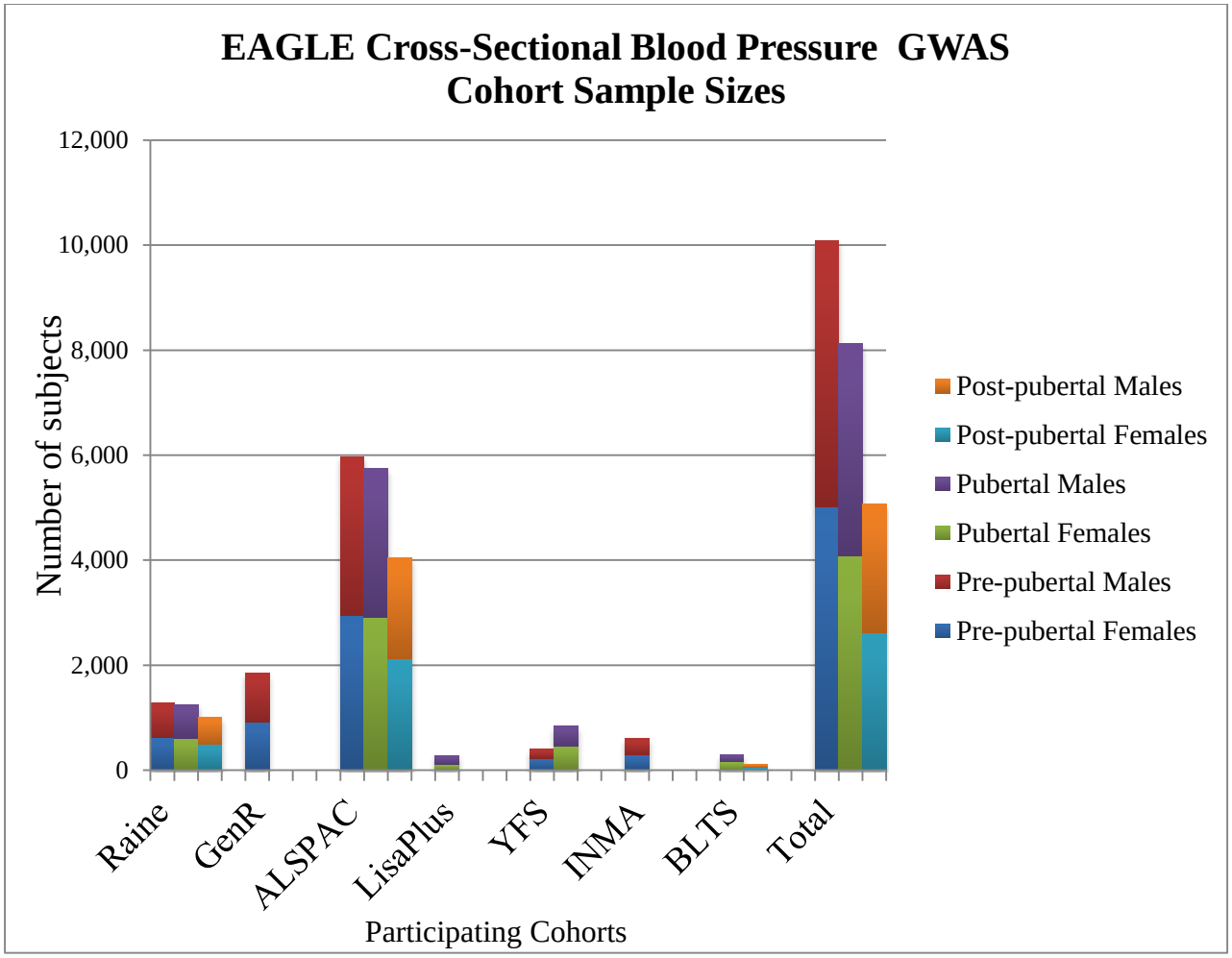
		Systolic Blood Pressure	
SNP or Gene	Related to human BP	Animal model with BP or vascular phenotype or regional linkage to BP?	Relationship of gene, region, SNP or gene product with another disease [GeneCards]
rs13025174			
TMEM247			
FSHR		Vascular responses in male and female hypertensive rates with hyperhomocysteinemia[63]	Regulation of systemic arterial blood pressure
rs1383450			
rs276978			
XKR4		Variants in XKR4 are involved in the regulation of thyroid-stimulating hormone[64]	
LAMP5			
rs28601630			
MTMR3		MTMR3 was correlated with lipid metabolism and potential mediator of miR-4513, which is significantly associated with fasting glucose, LDL and total cholesterol, and blood pressure[65]	
HORMAD2-AS1			
HORMAD2			
LOC105372988			

Supplementary Table 15: Summary known BP (and BP-related effects) for significant genes and variants associated with SBP in sex-combined meta-analysis across EAGLE (look-up across all epochs).

		Diastolic Blood Pressure	
SNP or Gene	Related to human BP	Animal model with BP or vascular phenotype or regional linkage to BP?	Relationship of gene, region, SNP or gene product with another disease [GeneCards]
CCDC141			mRNA expression in embryonic tissues in the endothelium of cardiovascular system
rs12542146			
rs9373002			
rs2944782			
LOC105373766			
rs734335			
POT1		Is an important molecular marker for biological aging, and is used as a proxy for potential risk predictors for cardiovascular disease[66]	

Supplementary Table 16: Summary known BP (and BP-related effects) for significant genes and variants associated with DBP in sex-combined meta-analysis across EAGLE (look-up across all epochs).

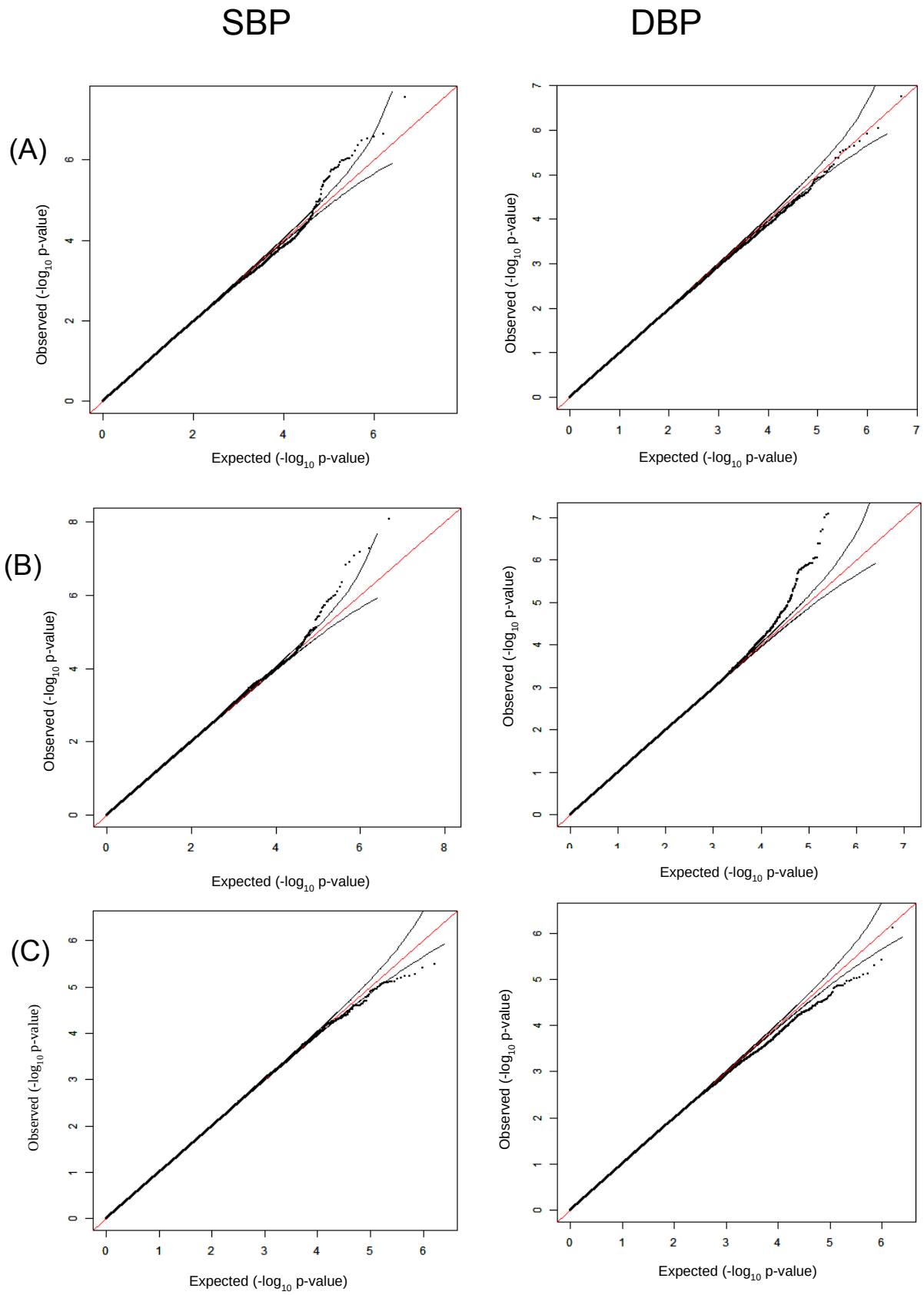
Supplementary Figures



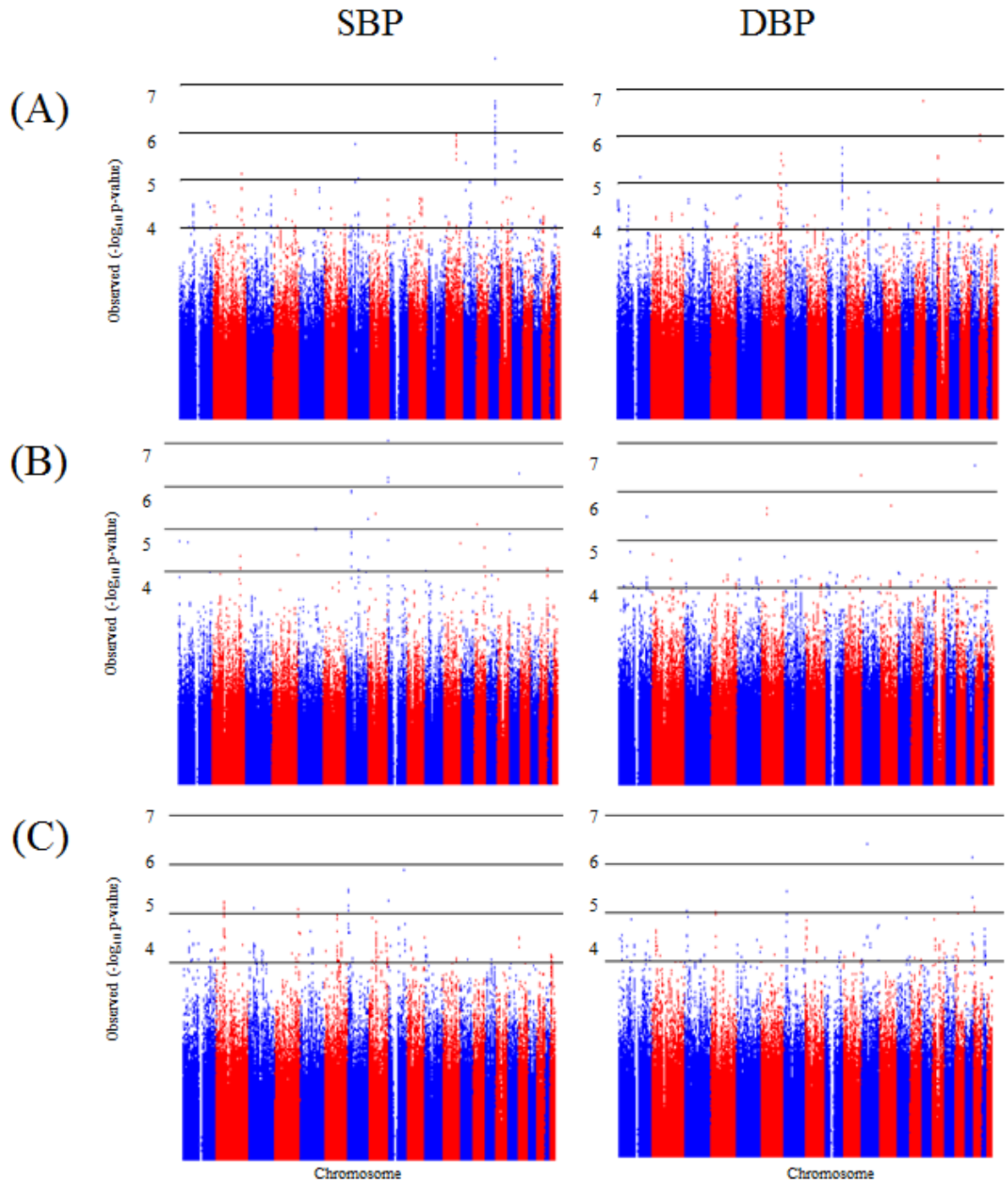
Supplementary Figure 1: Bar graph illustrating the number of subjects per cohort per timeframe used in analyses.

Pre-puberty [4-7 years], Puberty [8-12 years], Post-puberty [13-20 years]

Raine; The Western Australian Pregnancy (**Raine**) Cohort, Perth, Western Australia. **GenR;** The **Generation R** Study Group, Rotterdam, The Netherlands**. ALSPAC;** The **A**von **L**ongitudinal **S**tudy of **P**arents and **C**hildren Bristol, UK**. Lisa Plus;** Influence of **l**ife-style factors on the development of the **i**mmune **s**ystem and **a**llergies in East and West Germany **Plus** the influence of traffic emissions and genetics, Neuherberg, Germany. **YFS;** The Cardiovascular Risk in **Y**oung **F**inns **S**tudy, Turku, Finland **. INMA;** Spanish INMA—**IN**fancia y **M**edio **A**mbiente, Barcelona, Catalonia, Spain. **BLTS;** Brisbane Longitudinal Twin Study, Brisbane, Queensland, Australia

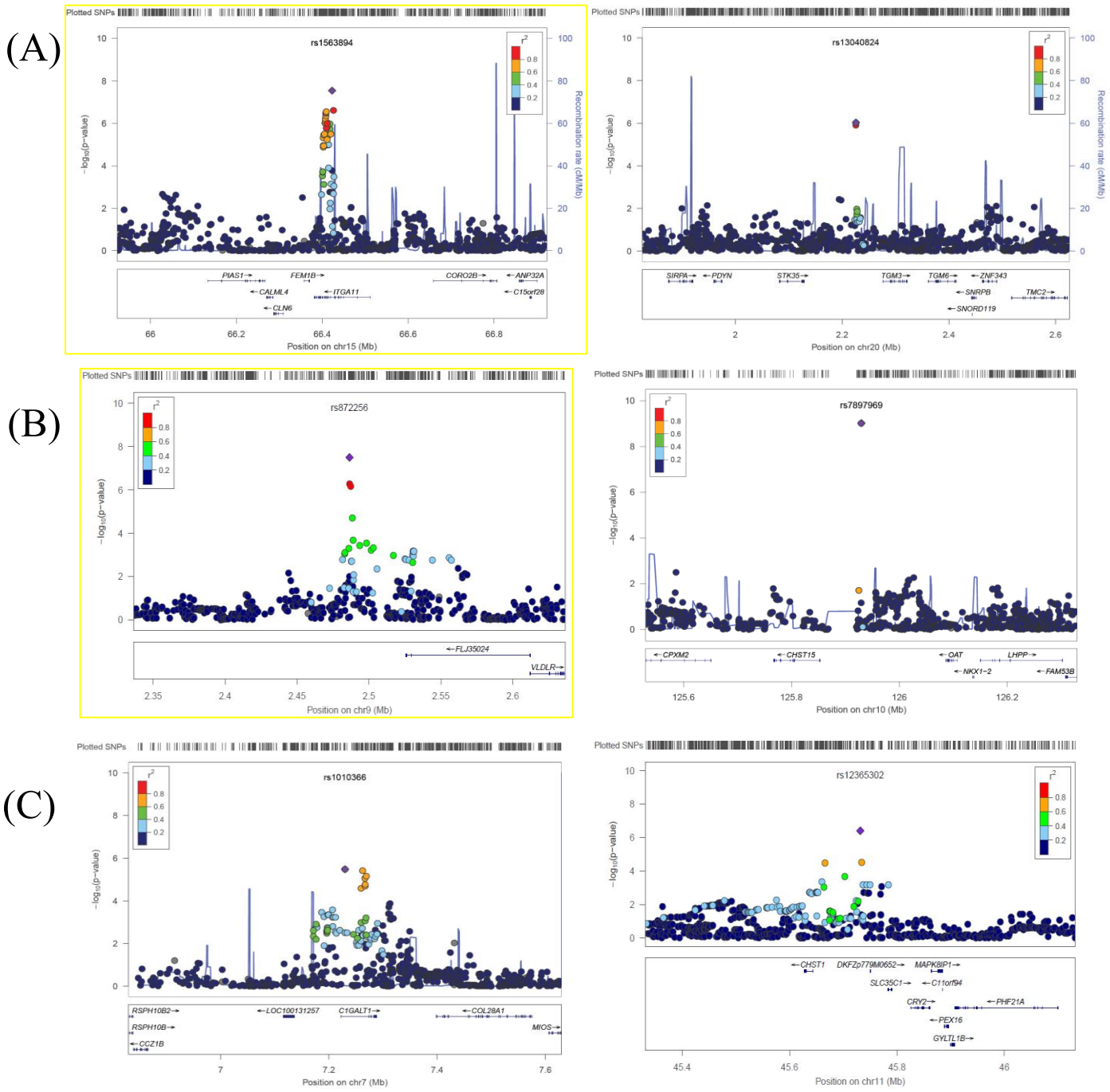


Supplementary Figure 2: Pre-Pubertal QQ plots for meta-analysis of association studies. The red line has a slope of 1 and an intercept of 0. The black lines are the 95% Confidence Interval and the association statistics are plotted as points. Plots shown on left represent Systolic Blood Pressure and plots on right represent Diastolic Blood Pressure. Rows represent: (A) Pre-pubertal, (B) Pubertal and (C) Post-pubertal (Sex-combined).



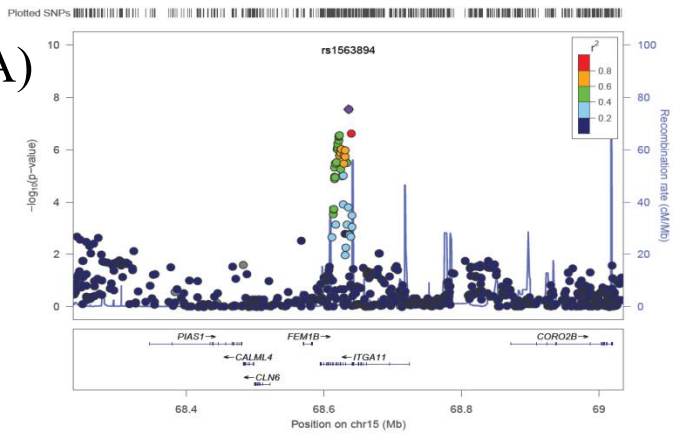
Supplementary Figure 3: Manhattan Plots. Plots shown on left represent Systolic Blood Pressure and plots on right represent Diastolic Blood Pressure. Rows represent: (A) Pre-pubertal, (B) Pubertal and (C) Post-pubertal (Sex-combined)

SBP DBP

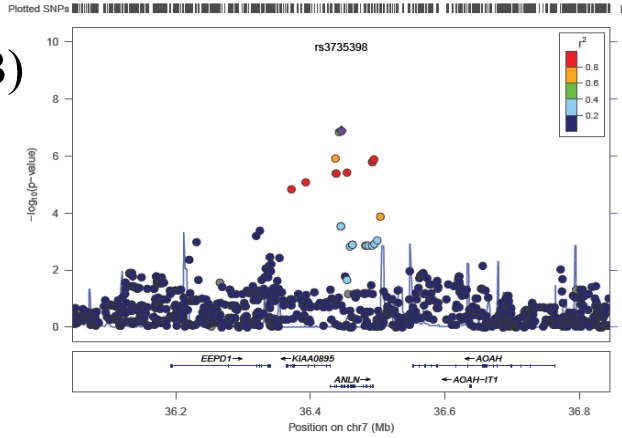


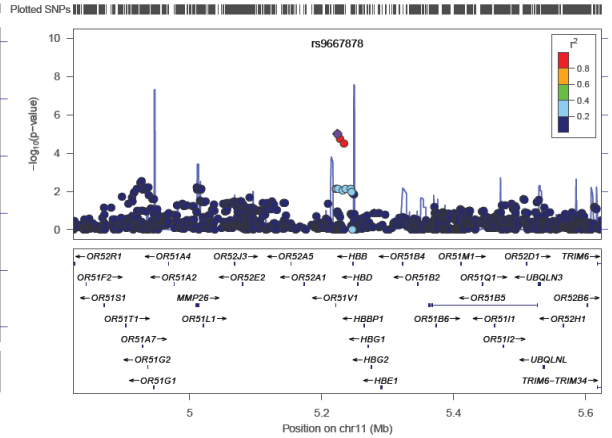
Supplementary Figure 4: Regional Association Plots for most significant 'SNP' finding per blood pressure outcome and epoch. –log10 (*p-values*) are shown for all SNPs in the region and colour of circles indicates degree of LD with the most associated SNP in the region. Plots shown on left represent Plots shown on left represent Systolic Blood Pressure and plots on right represent Diastolic Blood Pressure. Rows represent: (A) Pre-pubertal, (B) Pubertal and (C) Post-Pubertal (Sex-combined). Regional plots boxed in yellow indicate SNP effects that reached genome-wide levels of significance (5×10^{-8}).

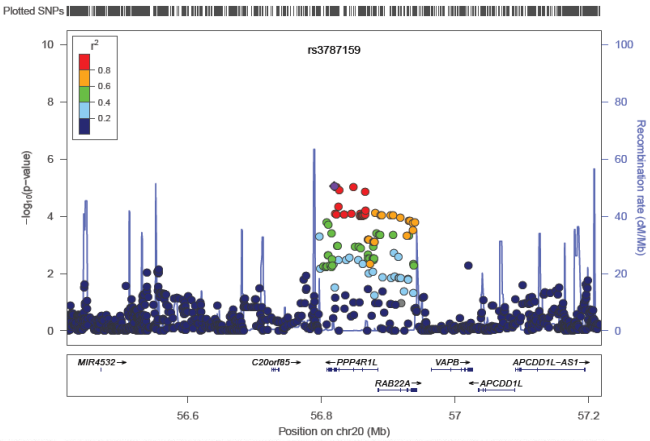
(A)


Plotted SNPs
rs1563894
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
PIAS1
FEM1B
CORO2B
CALML4
ITGA11
CLN6
68.4
68.6
68.8
69
Position on chr15 (Mb)

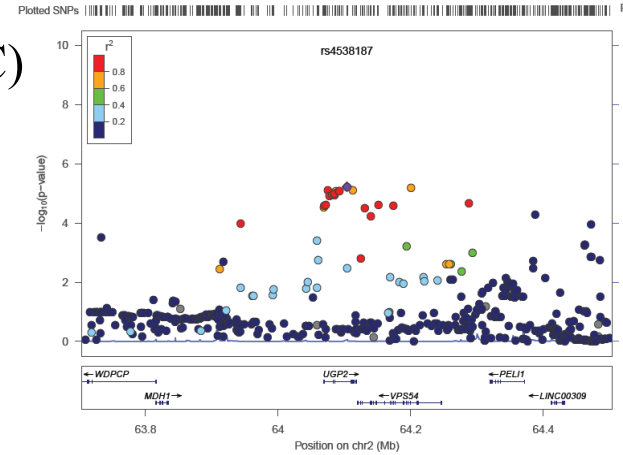
(B)

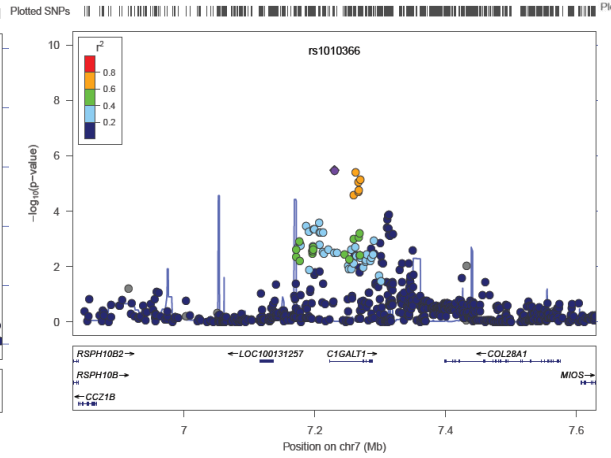

Plotted SNPs
rs3735398
−log10(p−value)
EEPD1
KIAA0895
AOAH
ANLN
AOAH−IT1
36.2
36.4
36.6
36.8
Position on chr7 (Mb)

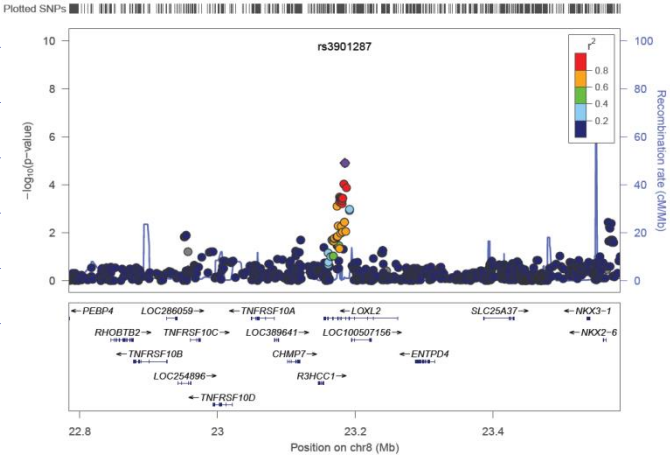

Plotted SNPs
rs9667878
−log10(p−value)
OR52R1
OR51A4
OR52J3
OR52A5
HBB
OR51B4
OR51M1
OR52D1
TRIM6
OR51F2
OR51A2
OR52E2
OR52A1
HBD
OR51B2
OR51Q1
UBQLN3
OR51S1
MMP26
OR51V1
OR51B5
OR52B6
OR51T1
OR51L1
HBBP1
OR51B6
OR51I1
OR52H1
OR51A7
HBG1
OR51I2
OR51G2
HBG2
UBQLNL
OR51G1
HBE1
TRIM6−TRIM34
5
5.2
5.4
5.6
Position on chr11 (Mb)


Plotted SNPs
rs3787159
−log10(p−value)
Recombination rate (cM/Mb)
MIR4532
C20orf85
PPP4R1L
VAPB
APCDD1L−AS1
RAB22A
APCDD1L
56.6
56.8
57
57.2
Position on chr20 (Mb)

(C)

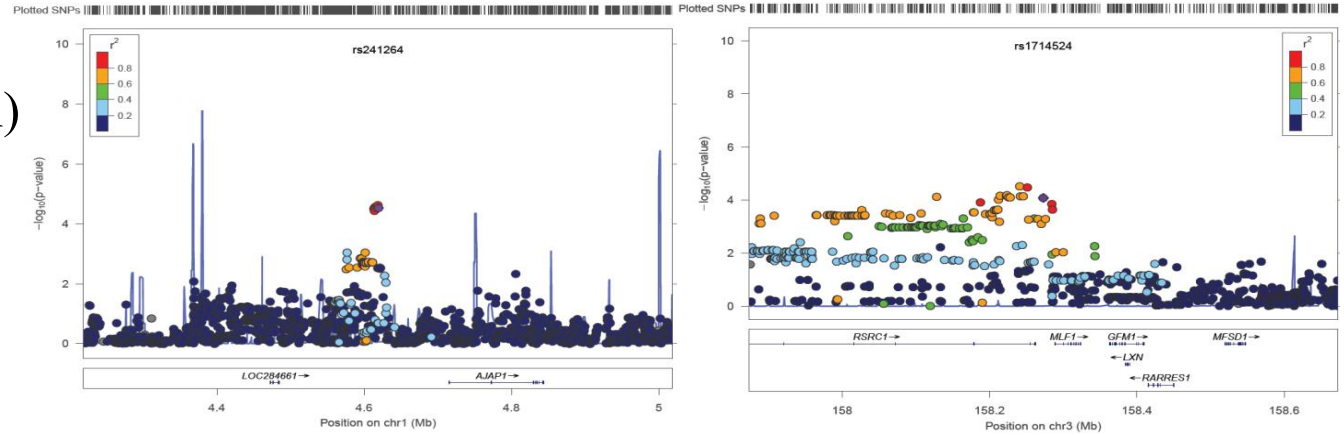

Plotted SNPs
rs4538187
−log10(p−value)
WDPCP
UGP2
PELI1
MDH1
VPS54
LINC00309
63.8
64
64.2
64.4
Position on chr2 (Mb)


Plotted SNPs
rs1010366
−log10(p−value)
RSPH10B2
LOC100131257
C1GALT1
COL28A1
RSPH10B
MIOS
CCZ1B
7
7.2
7.4
7.6
Position on chr7 (Mb)

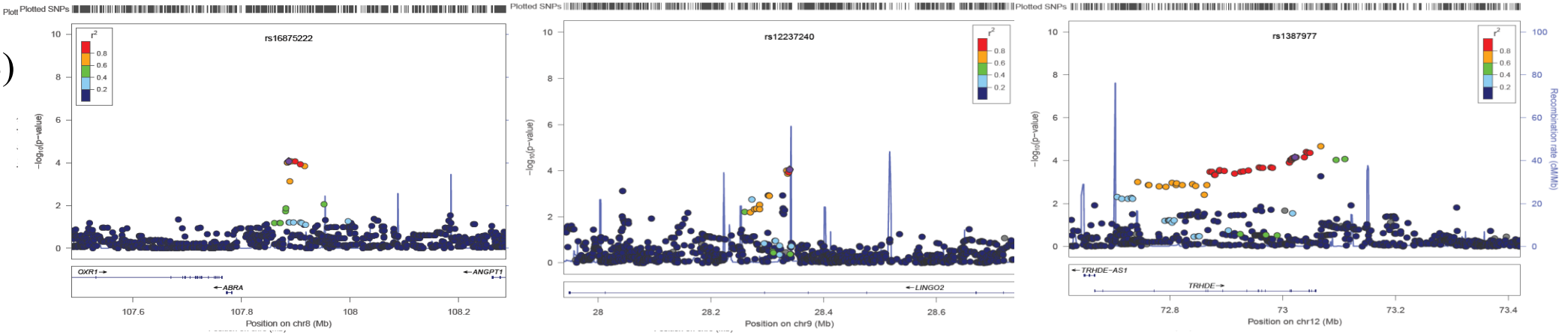

Plotted SNPs
rs3901287
−log10(p−value)
Recombination rate (cM/Mb)
PEBP4
LOC286059
TNFRSF10A
LOXL2
SLC25A37
NKX3−1
RHOBTB2
TNFRSF10C
LOC389641
LOC100507156
NKX2−6
TNFRSF10B
CHMP7
ENTPD4
LOC254896
R3HCC1
TNFRSF10D
22.8
23
23.2
23.4
Position on chr8 (Mb)

Supplementary Figure 5: Regional Association Plots for all 'SNP clusters' for SBP in sex-combined analyses –log10 (*p-values*) are shown for all SNPs in the region and colour of circles indicates degree of LD with the most associated SNP in the region. Plots shown on left represent Plots shown represent Systolic Blood Pressure. Rows represent: (A) Pre-pubertal, (B) Pubertal and (C) Post-pubertal.

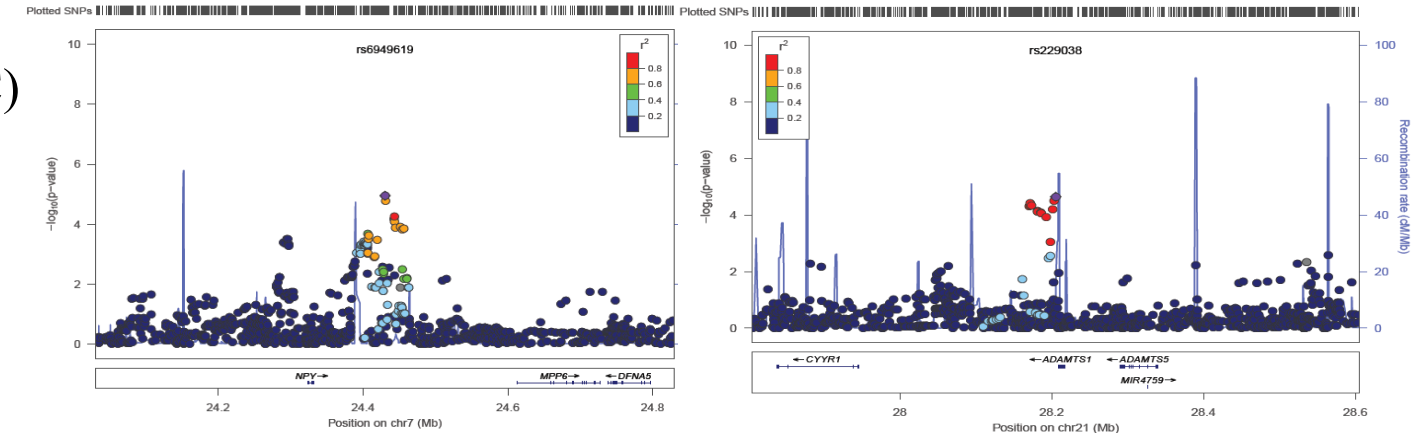
(A)


Plotted SNPs
rs241264
rs1714524
r²
0.8
0.6
0.4
0.2
−log10(p-value)
LOC284661
AJAP1
RSRC1
MLF1
GFM1
MFSD1
LXN
RARRES1
Position on chr1 (Mb)
Position on chr3 (Mb)

(B)

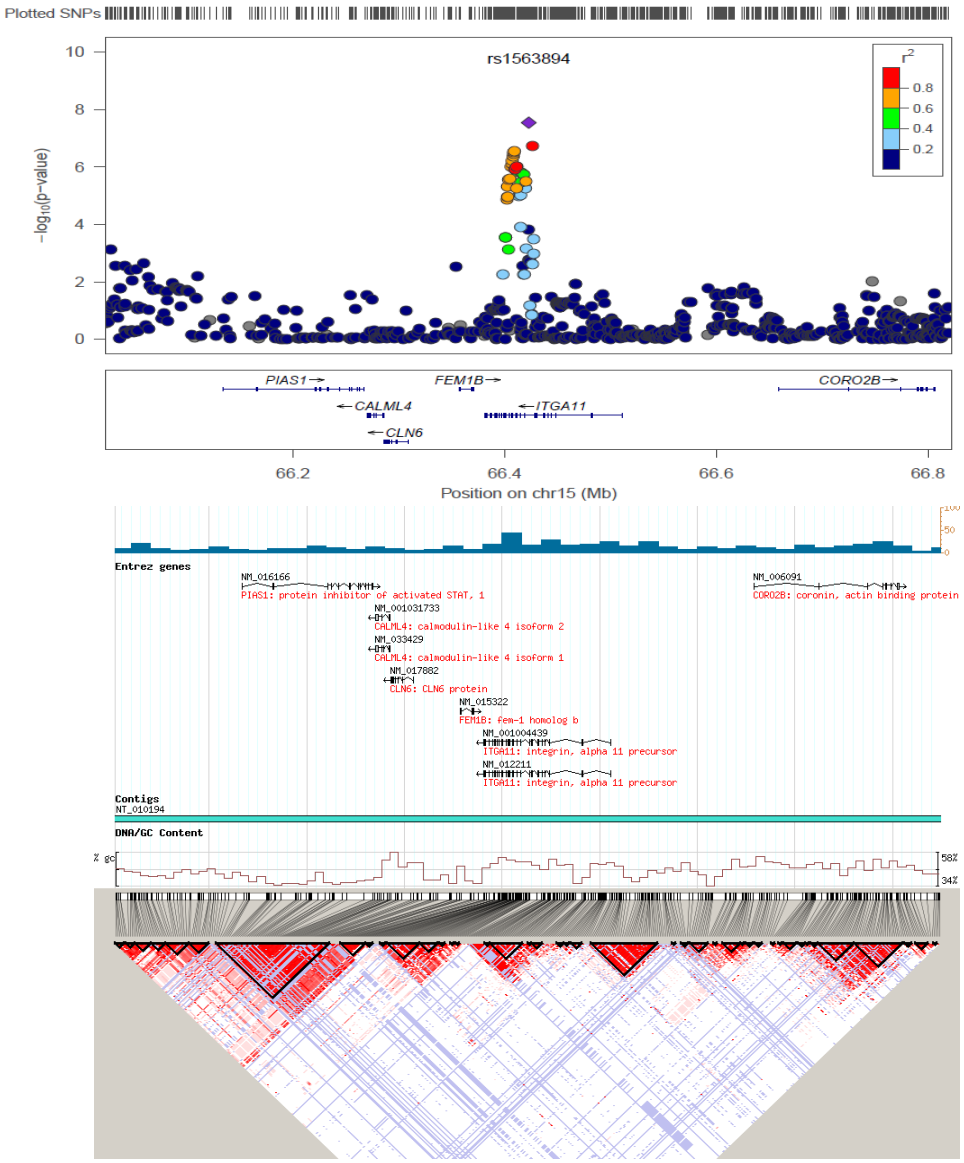

Plotted SNPs
rs16875222
rs12237240
rs1387977
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
OXR1
ANGPT1
ABRA
LINGO2
TRHDE-AS1
TRHDE
Position on chr8 (Mb)
Position on chr9 (Mb)
Position on chr12 (Mb)

(C)

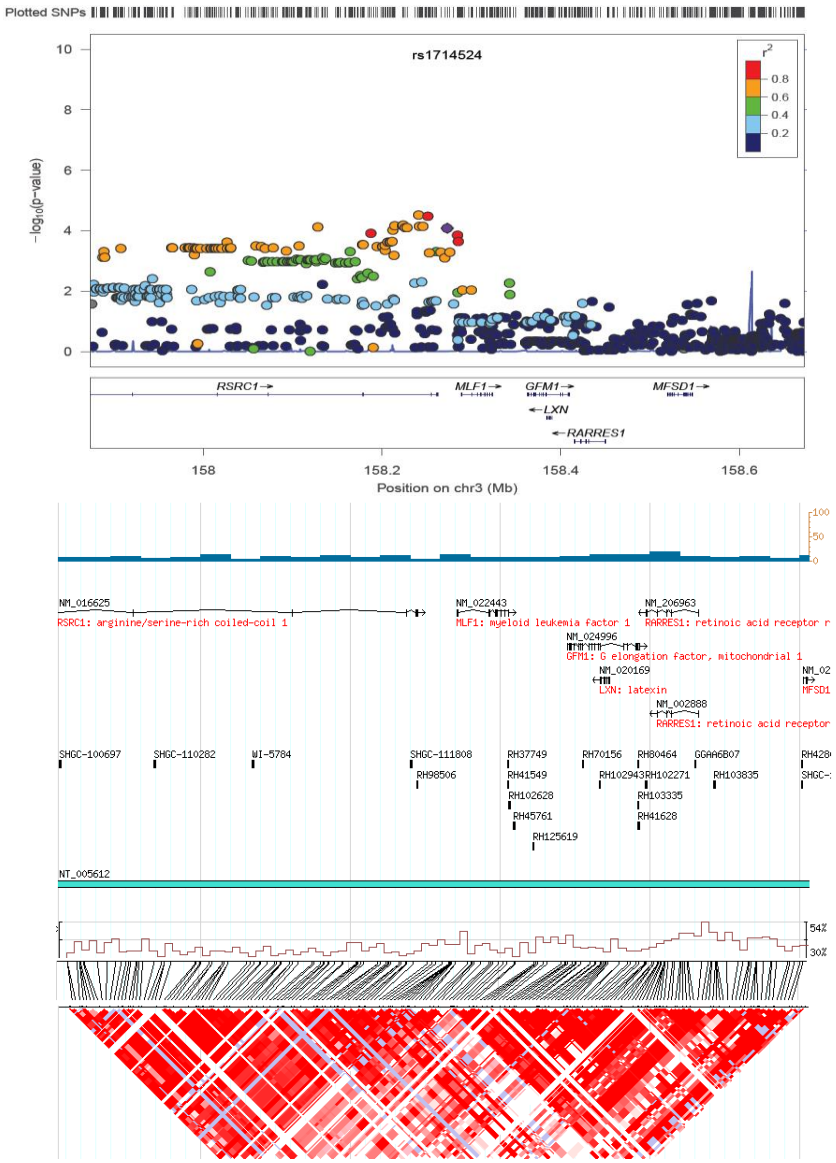

Plotted SNPs
rs6949619
rs229038
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
NPY
MPP6
DFNA5
CYYR1
ADAMTS1
ADAMTS5
MIR4759
Position on chr7 (Mb)
Position on chr21 (Mb)

Supplementary Figure 6: Regional Association Plots for all 'SNP clusters' for DBP in sex-combined analyses –log10 (*p-values*) are shown for all SNPs in the region and colour of circles indicates degree of LD with the most associated SNP in the region. Plots shown on left represent Plots shown represent Diastolic Blood Pressure. Rows represent: (A) Pre-pubertal, (B) Pubertal and (C) Post-pubertal.

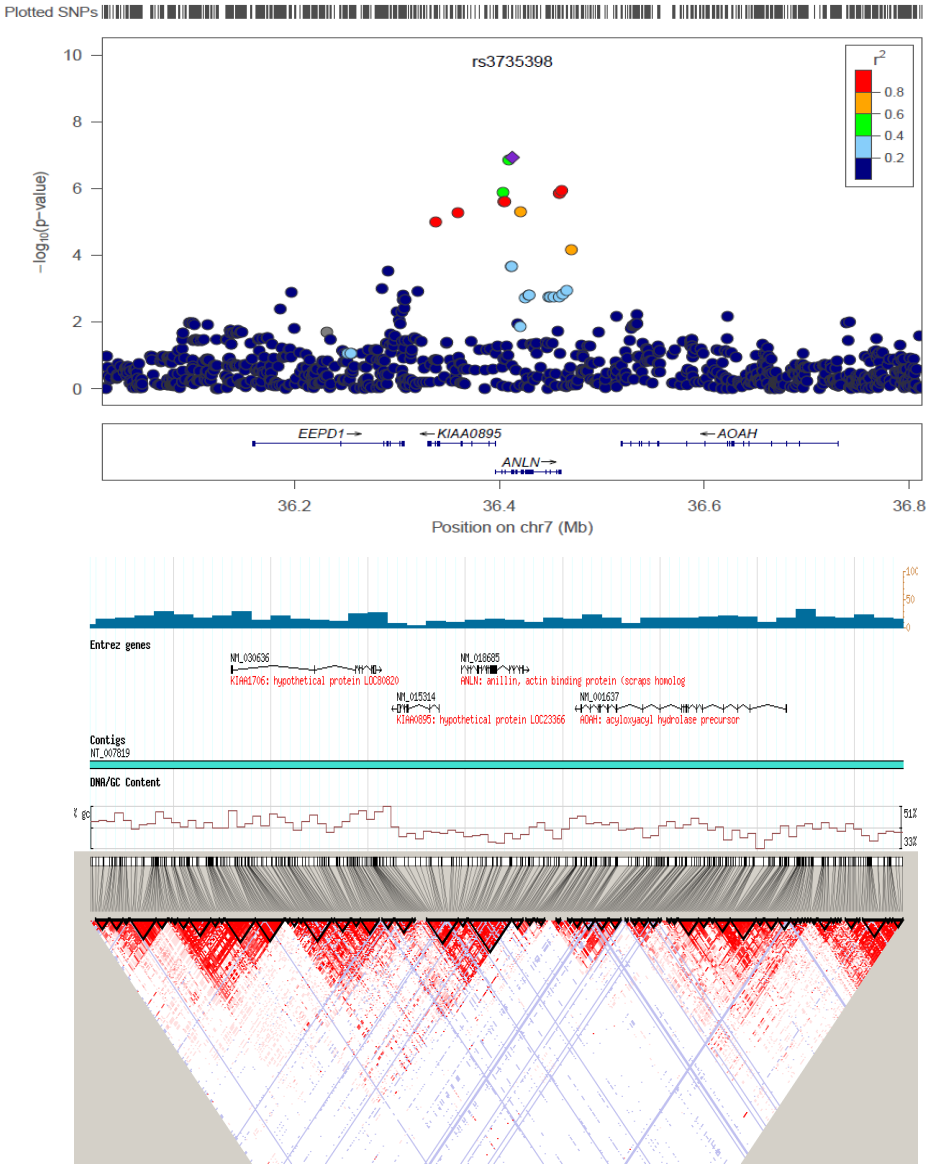
SBP

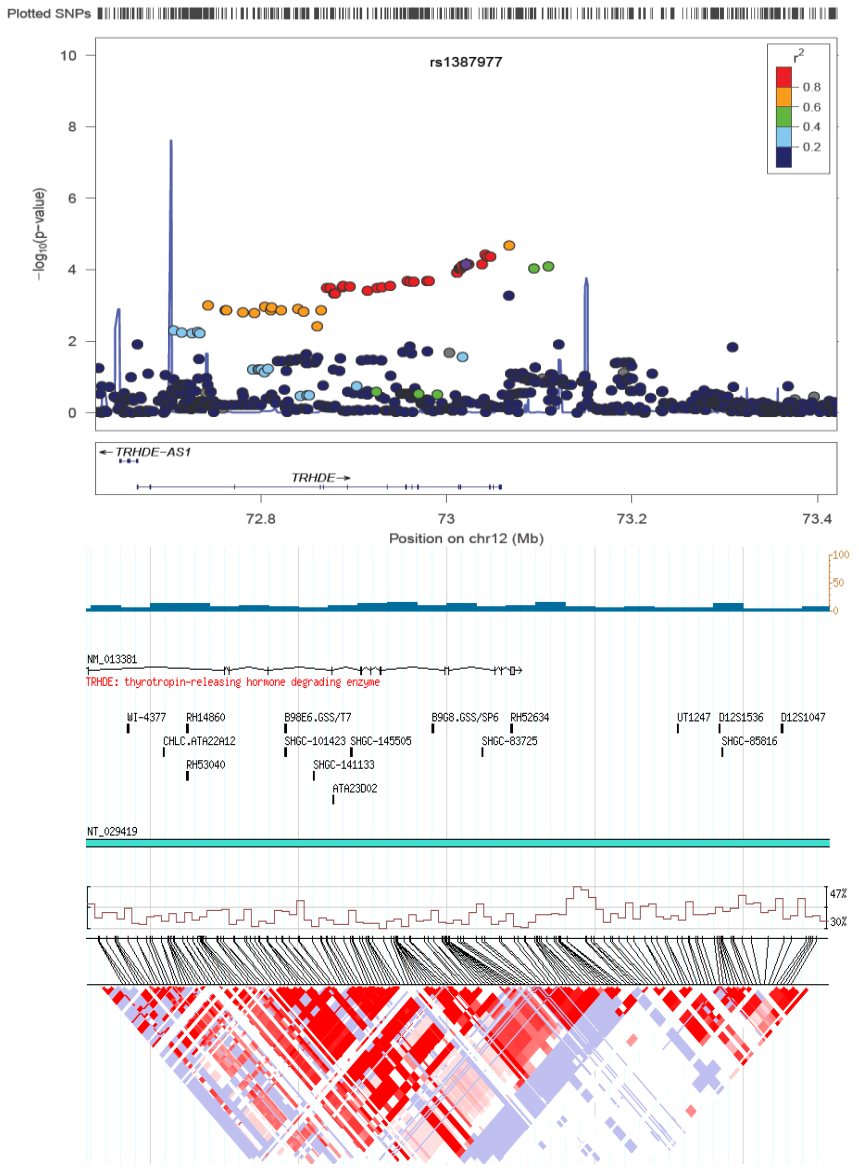

Plotted SNPs
rs1563894
$-\log_{10}$(p-value)
PIAS1
FEM1B
CORO2B
CALML4
ITGA11
CLN6
Position on chr15 (Mb)
Entrez genes
PIAS1: protein inhibitor of activated STAT, 1
CORO2B: coronin, actin binding protein
CALML4: calmodulin-like 4 isoform 2
CALML4: calmodulin-like 4 isoform 1
CLN6: CLN6 protein
FEM1B: fem-1 homolog b
ITGA11: integrin, alpha 11 precursor
Contigs
NT_010194
DNA/GC Content

DBP


Plotted SNPs
rs1714524
$-\log_{10}$(p-value)
RSRC1
MLF1
GFM1
MFSD1
LXN
RARRES1
Position on chr3 (Mb)
RSRC1: arginine/serine-rich coiled-coil 1
MLF1: myeloid leukemia factor 1
GFM1: G elongation factor, mitochondrial 1
LXN: latexin
RARRES1: retinoic acid receptor
NT_005612

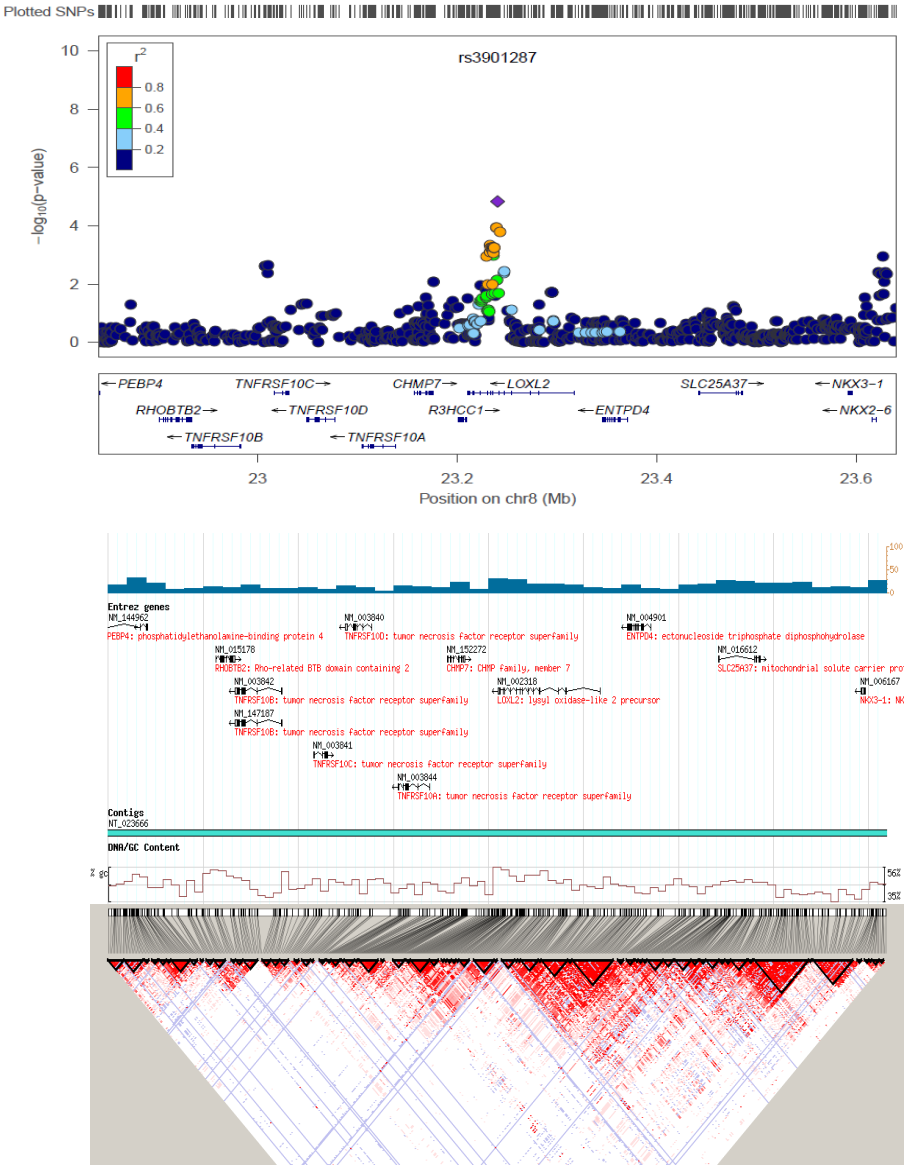
Supplementary Figure 7: Pre-Pubertal Regional Association Plots and Linkage Disequilibrium plots for significant SNP clusters. Regional association plots: –log10 (*p-values*) are shown for all SNPs in the region and colour of circles indicates degree of LD with the most associated SNP in the region. Recombination rates and LD (LOD scores in red) are plotted directly below. Plots shown on left represent Systolic Blood Pressure and plots on right represent Diastolic Blood Pressure (Sex-combined).


Plotted SNPs
rs3735398
r²
0.8
0.6
0.4
0.2
−log10(p-value)
EEPD1
KIAA0895
AOAH
ANLN
36.2
36.4
36.6
36.8
Position on chr7 (Mb)
Entrez genes
NM_030636
KIAA1706: hypothetical protein LOC80820
NM_018685
ANLN: anillin, actin binding protein (scraps homolog
NM_015314
KIAA0895: hypothetical protein LOC23366
NM_001637
AOAH: acyloxyacyl hydrolase precursor
Contigs
NT_007819
DNA/GC Content
51%
33%

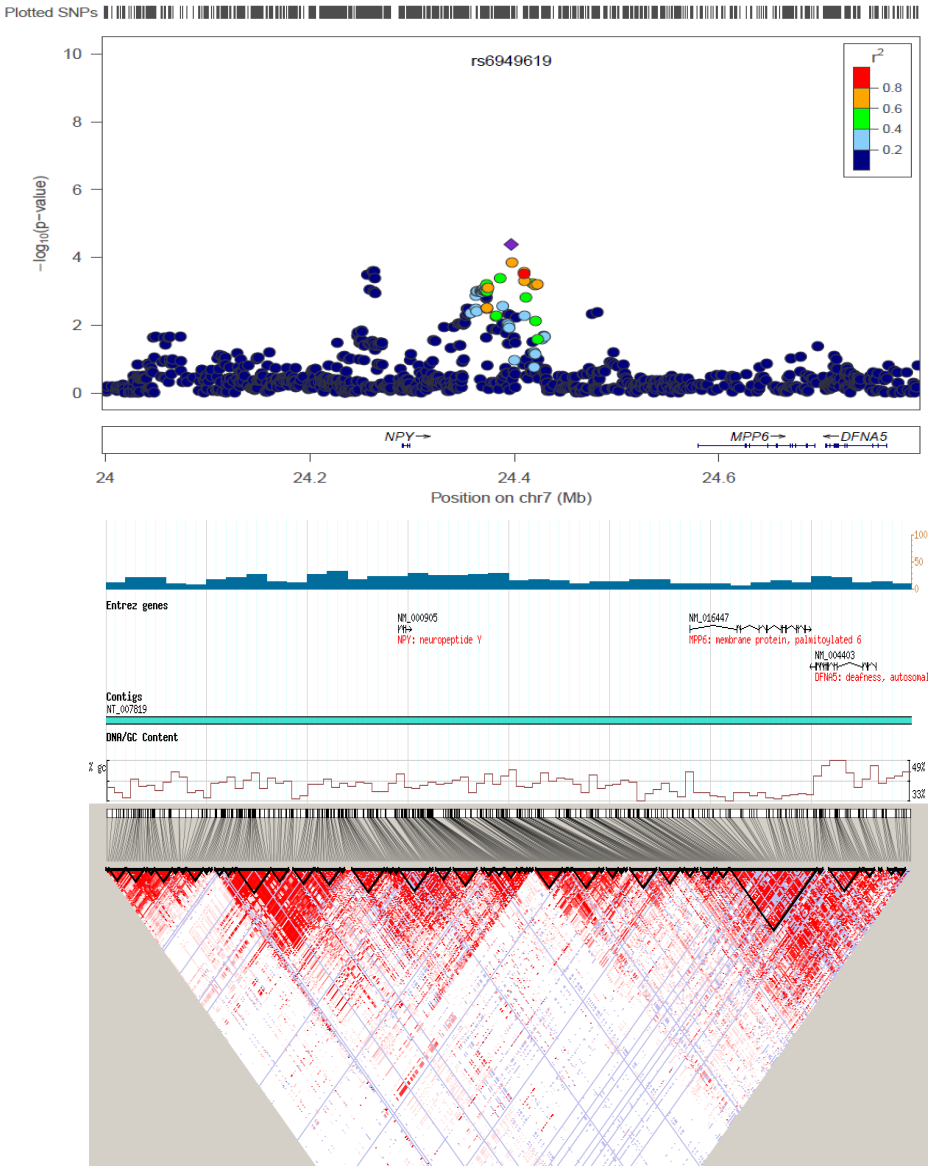

Plotted SNPs
rs1387977
r²
0.8
0.6
0.4
0.2
−log10(p-value)
TRHDE-AS1
TRHDE
72.8
73
73.2
73.4
Position on chr12 (Mb)
NM_013381
TRHDE: thyrotropin-releasing hormone degrading enzyme
WI-4377
RH14860
B98E6.GSS/T7
B96B.GSS/SP6
RH52634
UT1247
D12S1536
D12S1047
CHLC.ATA22A12
SHGC-101423
SHGC-145505
SHGC-83725
SHGC-85816
RH53040
SHGC-141133
ATA23D02
NT_029419
47%
30%

Supplementary Figure 8: Pubertal Regional Association Plots and Linkage Disequilibrium plots for significant SNP clusters. –log10 (*p-values*) are shown for all SNPs in the region and colour of circles indicates degree of LD with the most associated SNP in the region. Recombination rates and LD (LOD scores in red) are plotted directly below. Plots shown on left represent SBP as outcome and on right are DBP (Sex-combined).

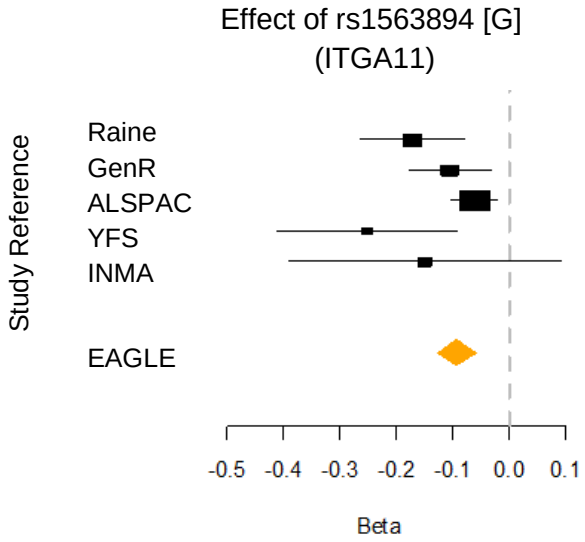
SBP


Plotted SNPs
rs3901287
r²
0.8
0.6
0.4
0.2
−log10(p−value)
PEBP4
TNFRSF10C
CHMP7
LOXL2
SLC25A37
NKX3−1
RHOBTB2
TNFRSF10D
R3HCC1
ENTPD4
NKX2−6
TNFRSF10B
TNFRSF10A
Position on chr8 (Mb)
Entrez genes
Contigs
DNA/GC Content

DBP

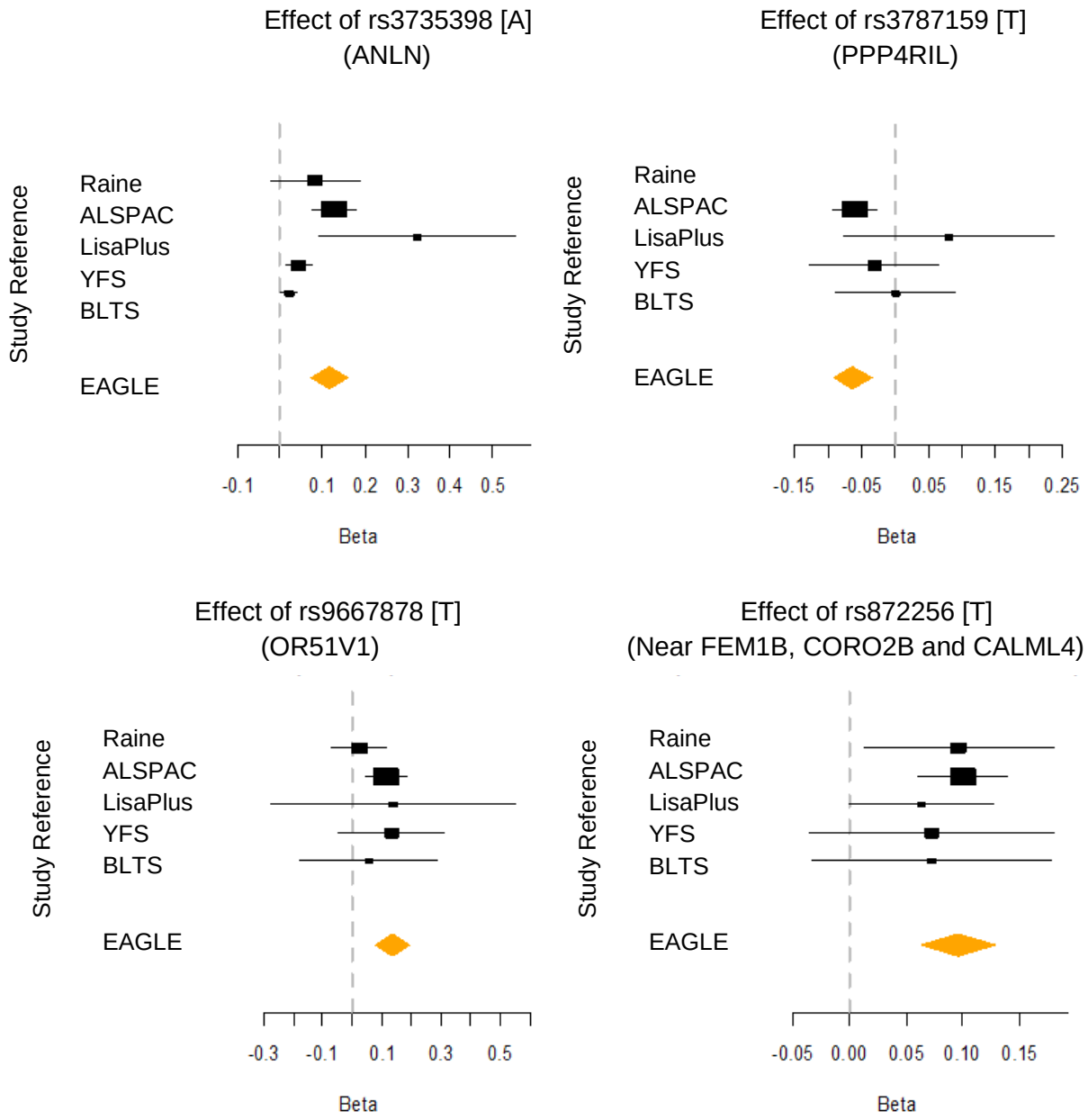

Plotted SNPs
rs6949619
r²
0.8
0.6
0.4
0.2
−log10(p−value)
NPY
MPP6
DFNA5
Position on chr7 (Mb)
Entrez genes
Contigs
DNA/GC Content

Supplementary Figure 9: Post-Pubertal Regional Association Plots and Linkage Disequilibrium plots for significant SNP clusters. –log10 (*p-values*) are shown for all SNPs in the region and colour of circles indicates degree of LD with the most associated SNP in the region. Recombination rates and LD (LOD scores in red) are plotted directly below. Plots shown on left represent SBP as outcome and on right are DBP (Sex-combined).



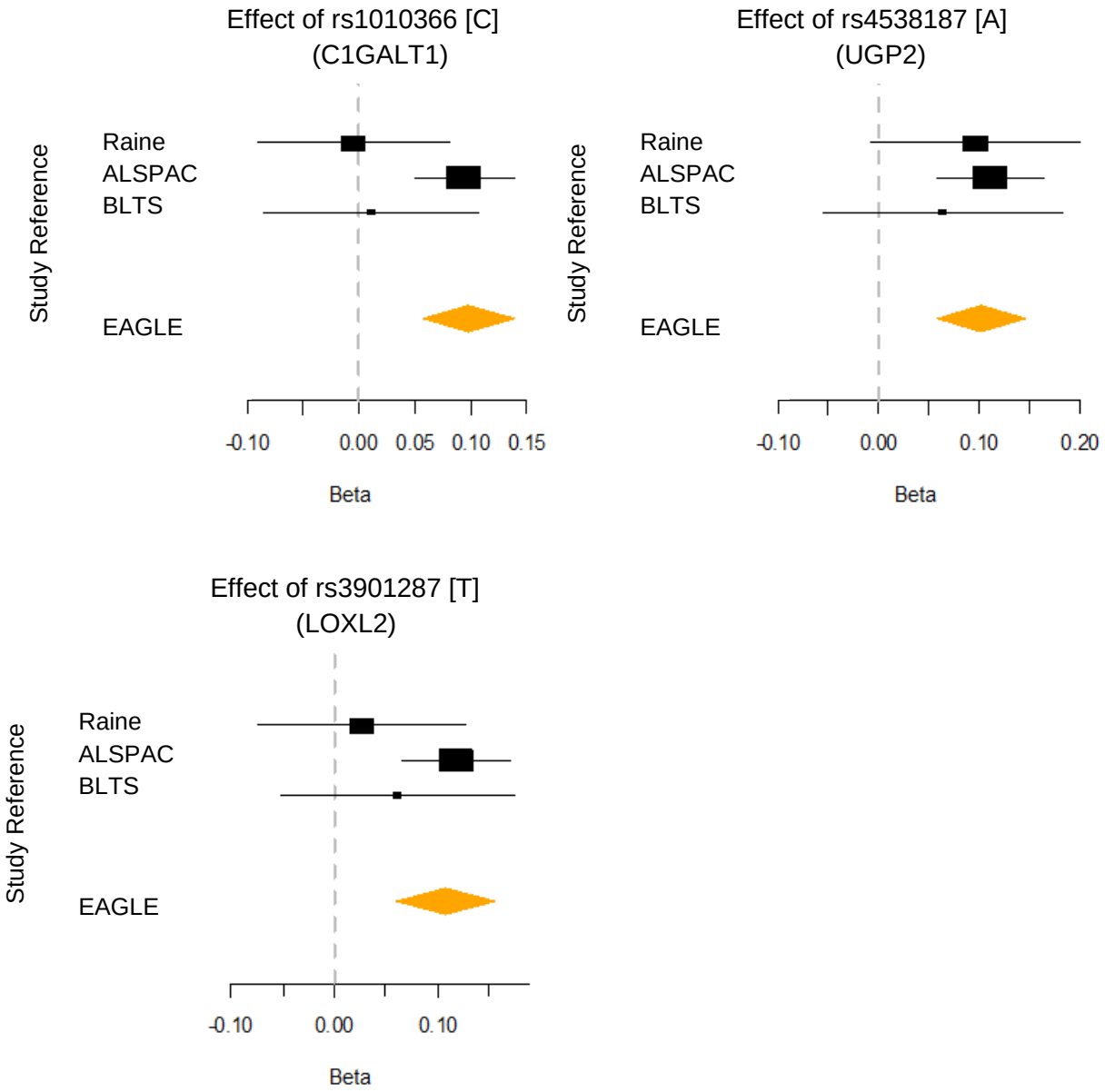
Supplementary Figure 10: Pre-Pubertal forest plots for all significant SNP clusters and/or most significant association resulting from sex-combined meta-analysis of SBP

Further detail relating to these variants can be found in Table 4.



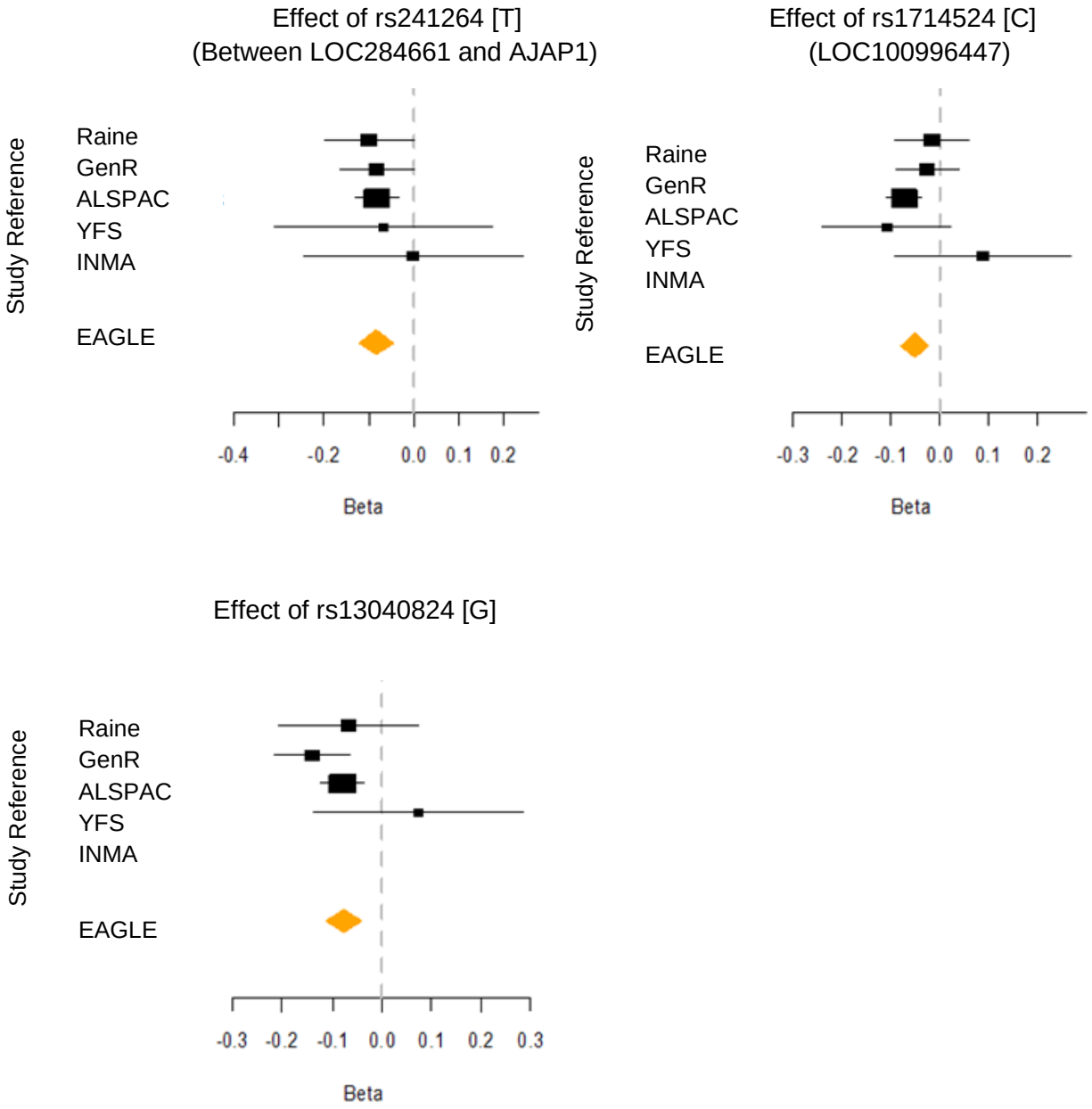
Supplementary Figure 11: Pubertal forest plots for all significant SNP clusters and/or most significant association resulting from sex-combined meta-analysis of SBP

Further detail relating to these variants can be found in Table 4.



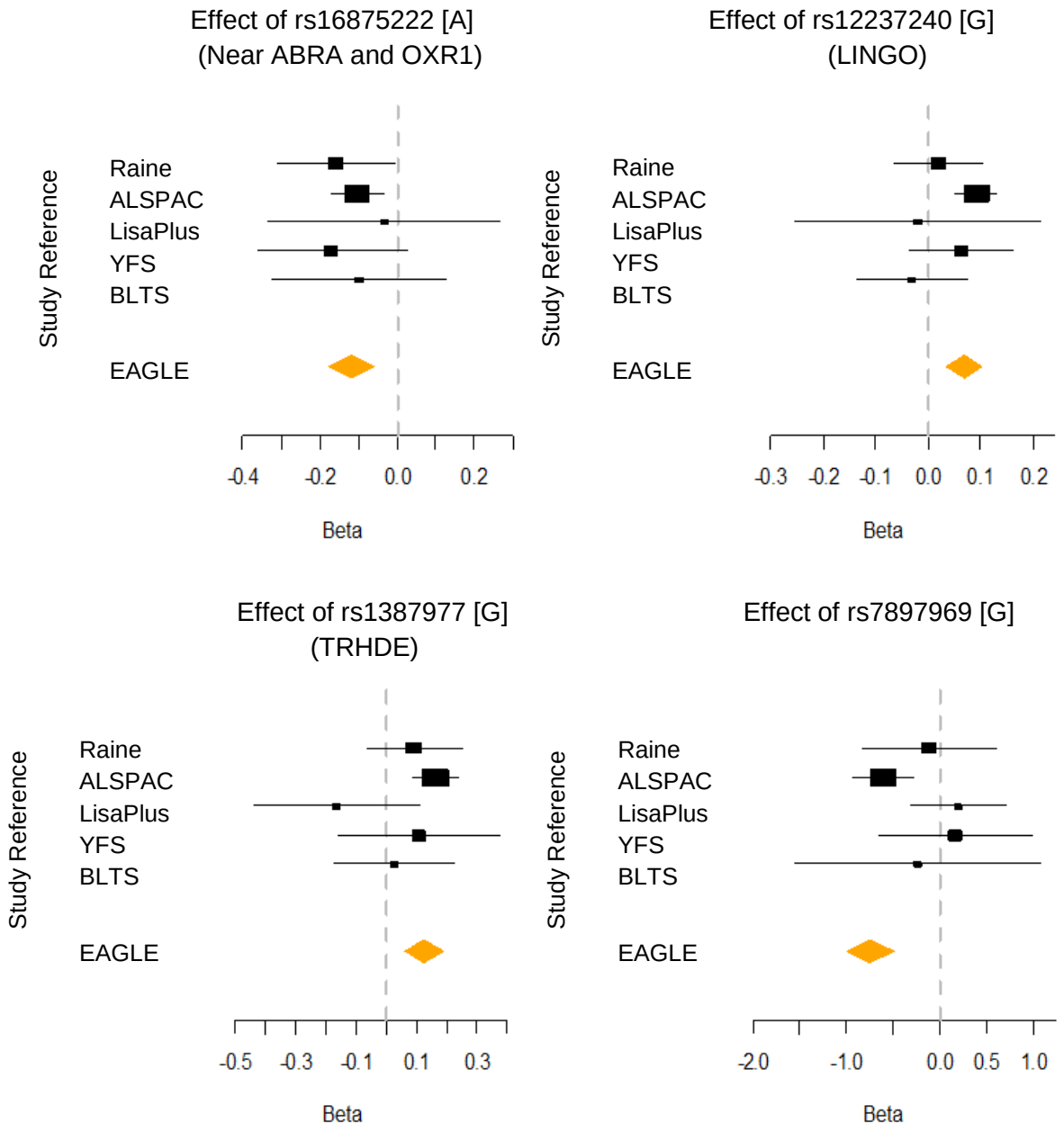
Supplementary Figure 12: Post-pubertal forest plots for all significant SNP clusters and/or most significant association resulting from sex-combined meta-analysis of SBP

Further detail relating to these variants can be found in Table 4.



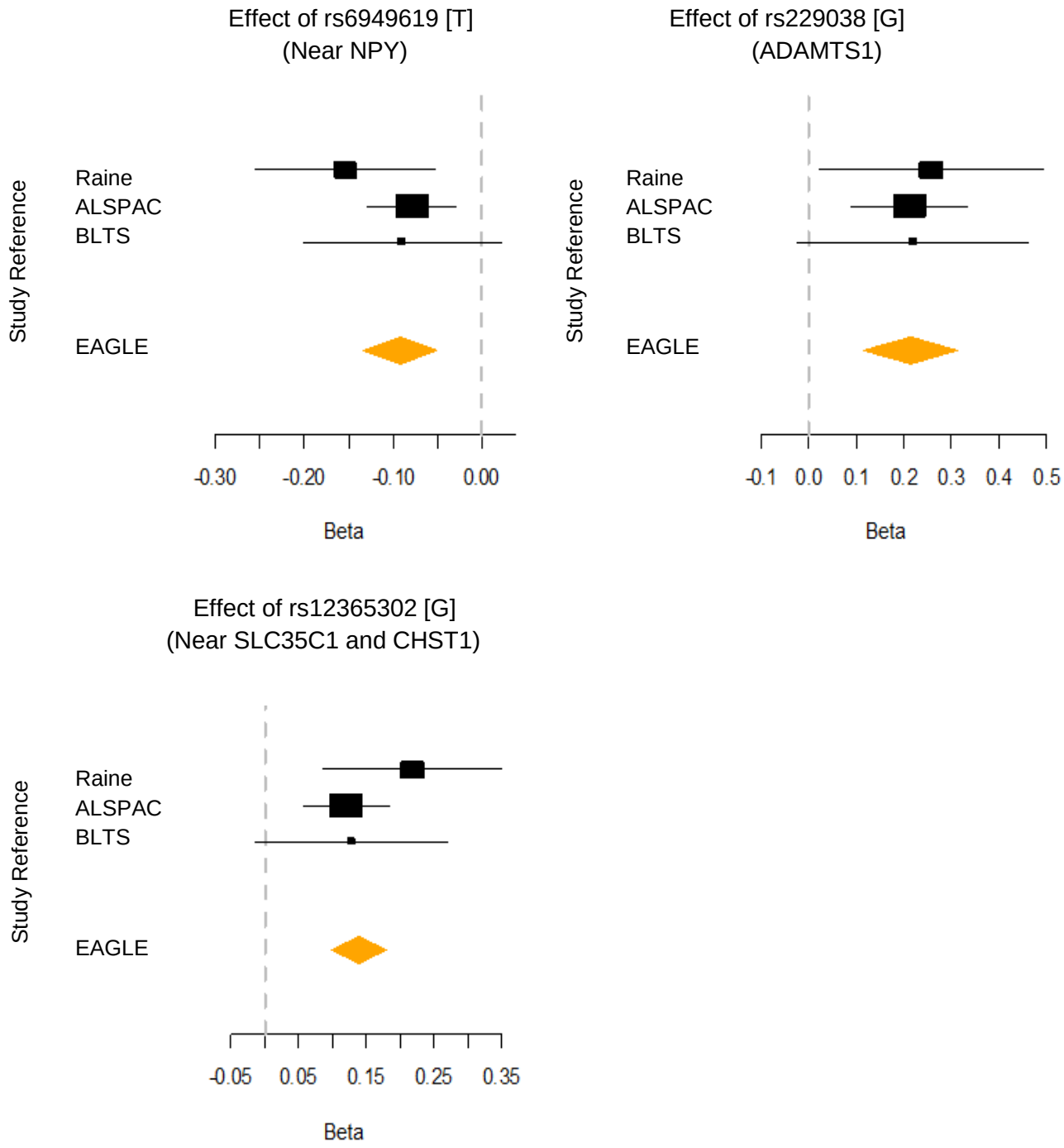
Supplementary Figure 13: Pre-Pubertal forest plots for all significant SNP clusters and/or most significant association resulting from sex-combined meta-analysis of DBP

Further detail relating to these variants can be found in Table 4.



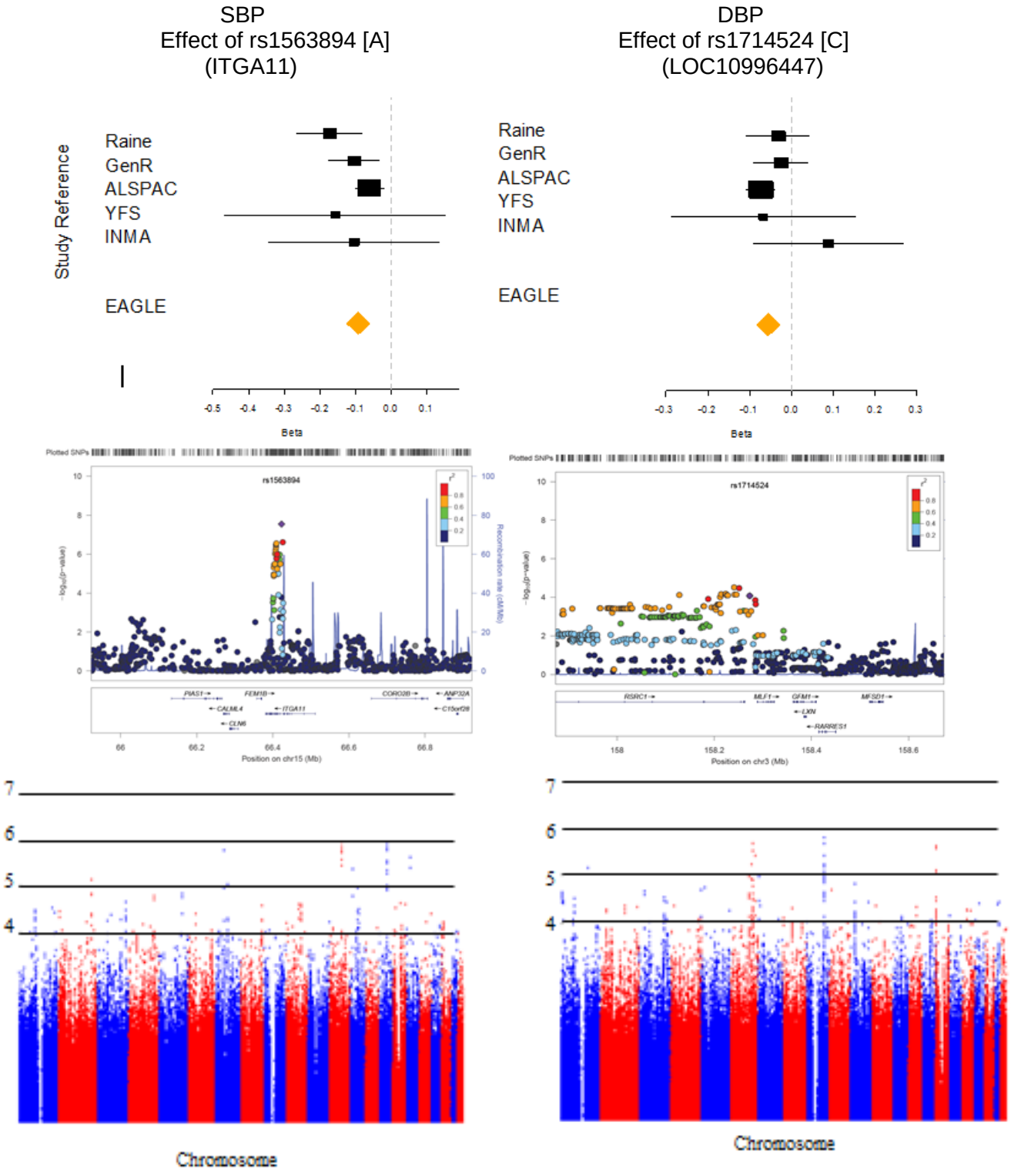
Supplementary Figure 14: Pubertal forest plots for all significant SNP clusters and/or most significant association resulting from sex-combined meta-analysis of DBP

Further detail relating to these variants can be found in Table 4.

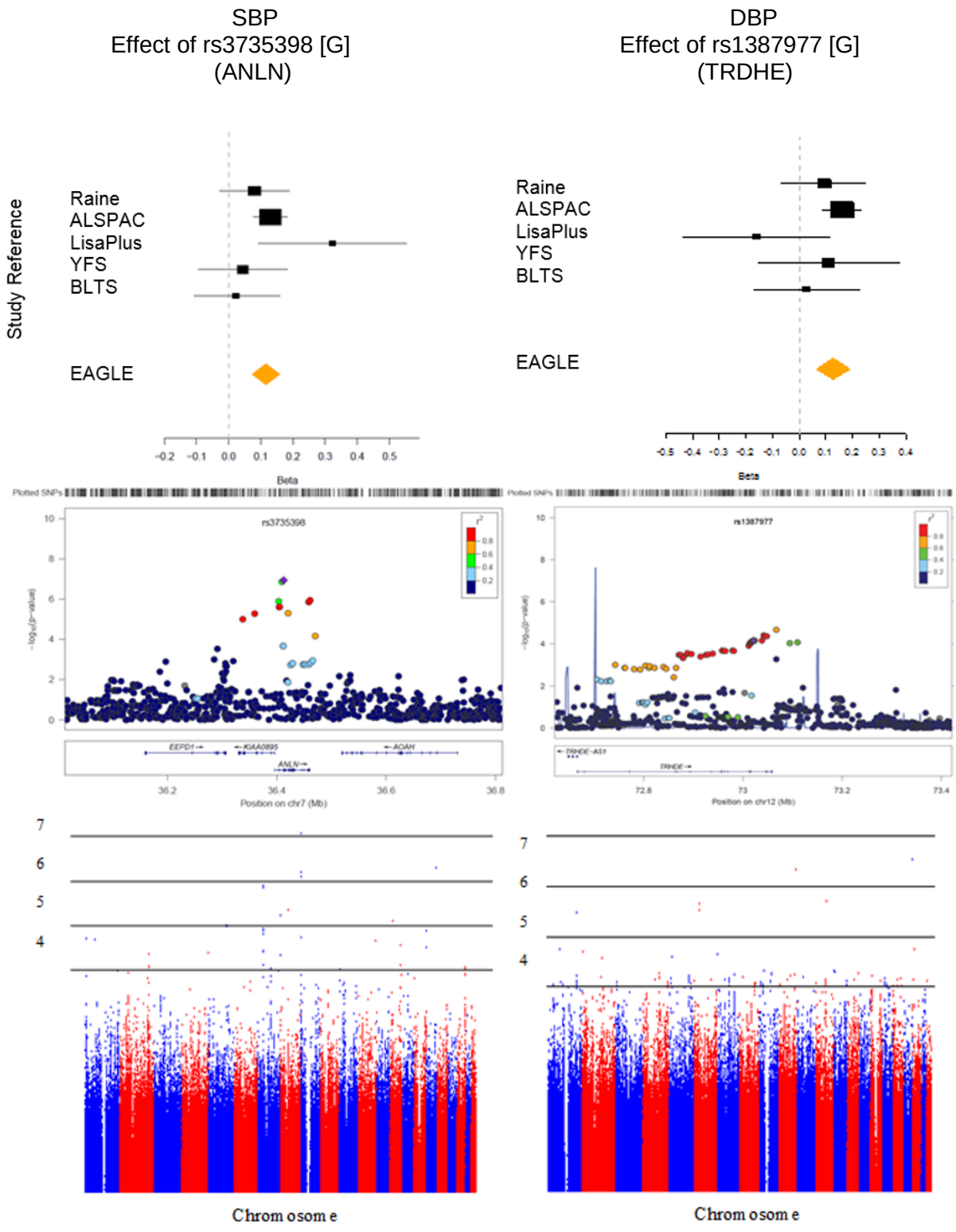


Supplementary Figure 15: Post-pubertal forest plots for all significant SNP clusters and/or most significant association resulting from sex-combined meta-analysis of DBP

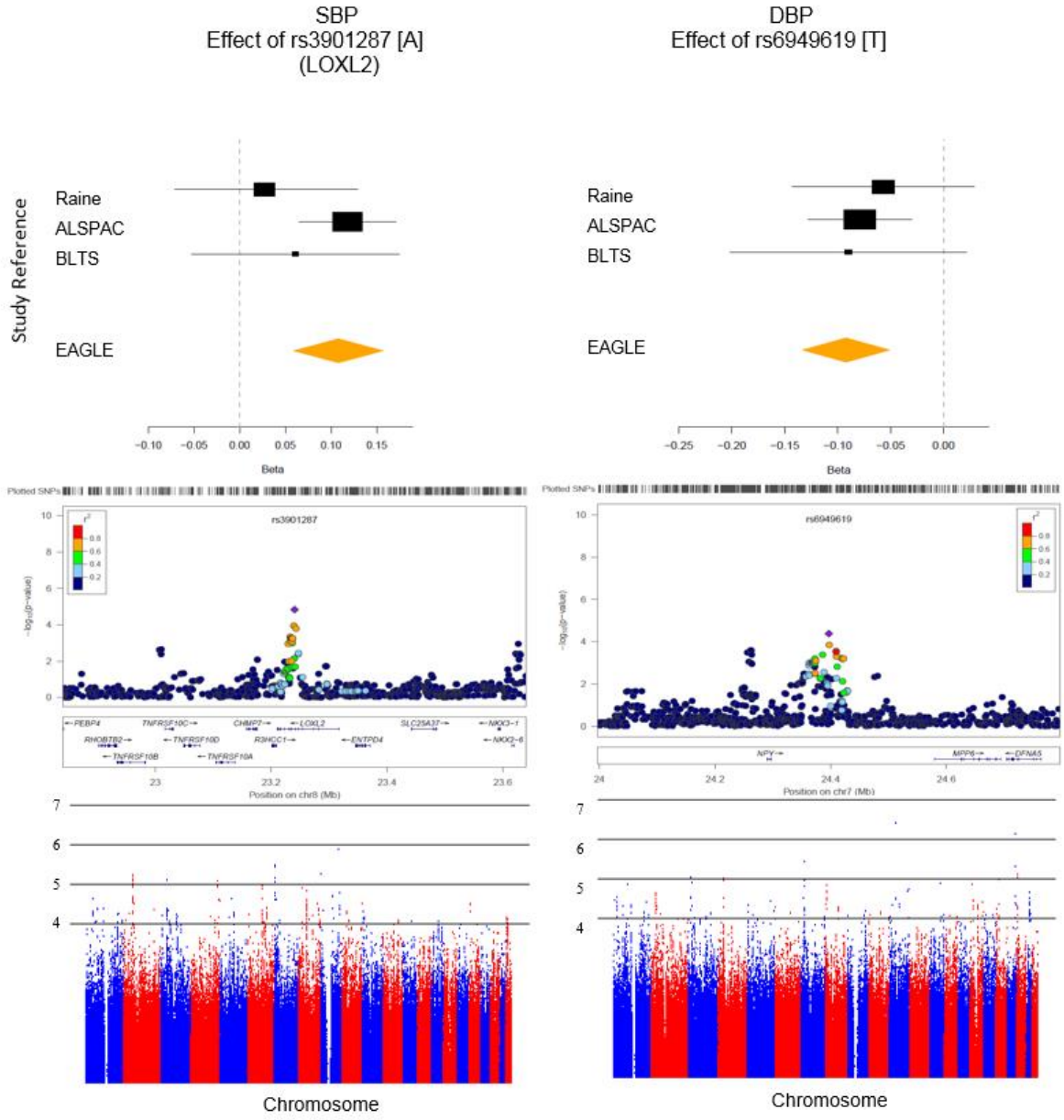
Further detail relating to these variants can be found in Table 4.



Supplementary Figure 16: Pre-pubertal sex-combined figure overview. From top to bottom: forest plot (top), regional association plot (center) and Manhattan plot (bottom).



Supplementary Figure 17: Pubertal sex-combined figure overview. From top to bottom: forest plot (top), regional association plot (center) and Manhattan plot (bottom).

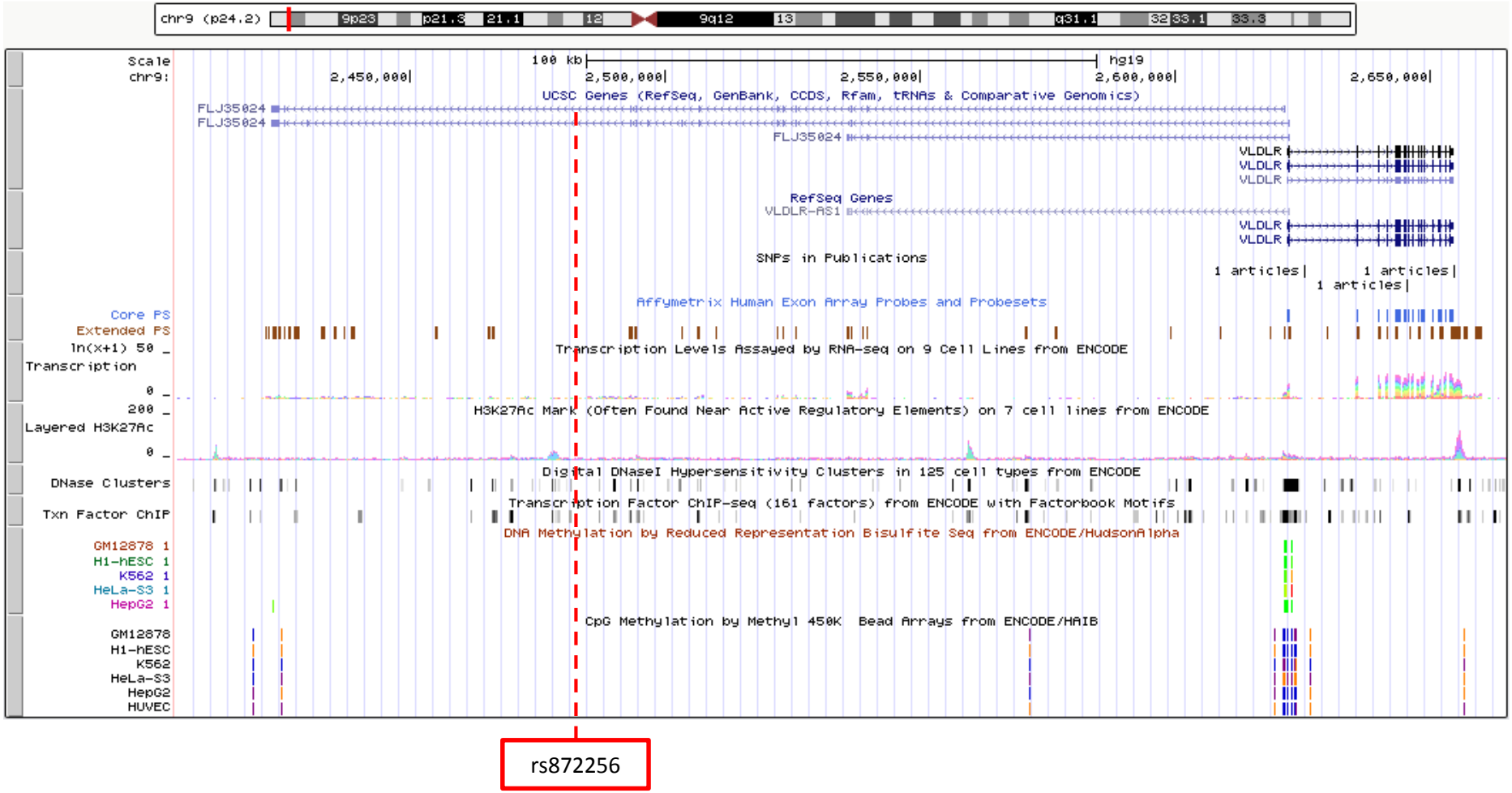


Supplementary Figure 18: Post-pubertal sex-combined figure overview. From top to bottom: forest plot (top), regional association plot (center) and Manhattan plot (bottom).

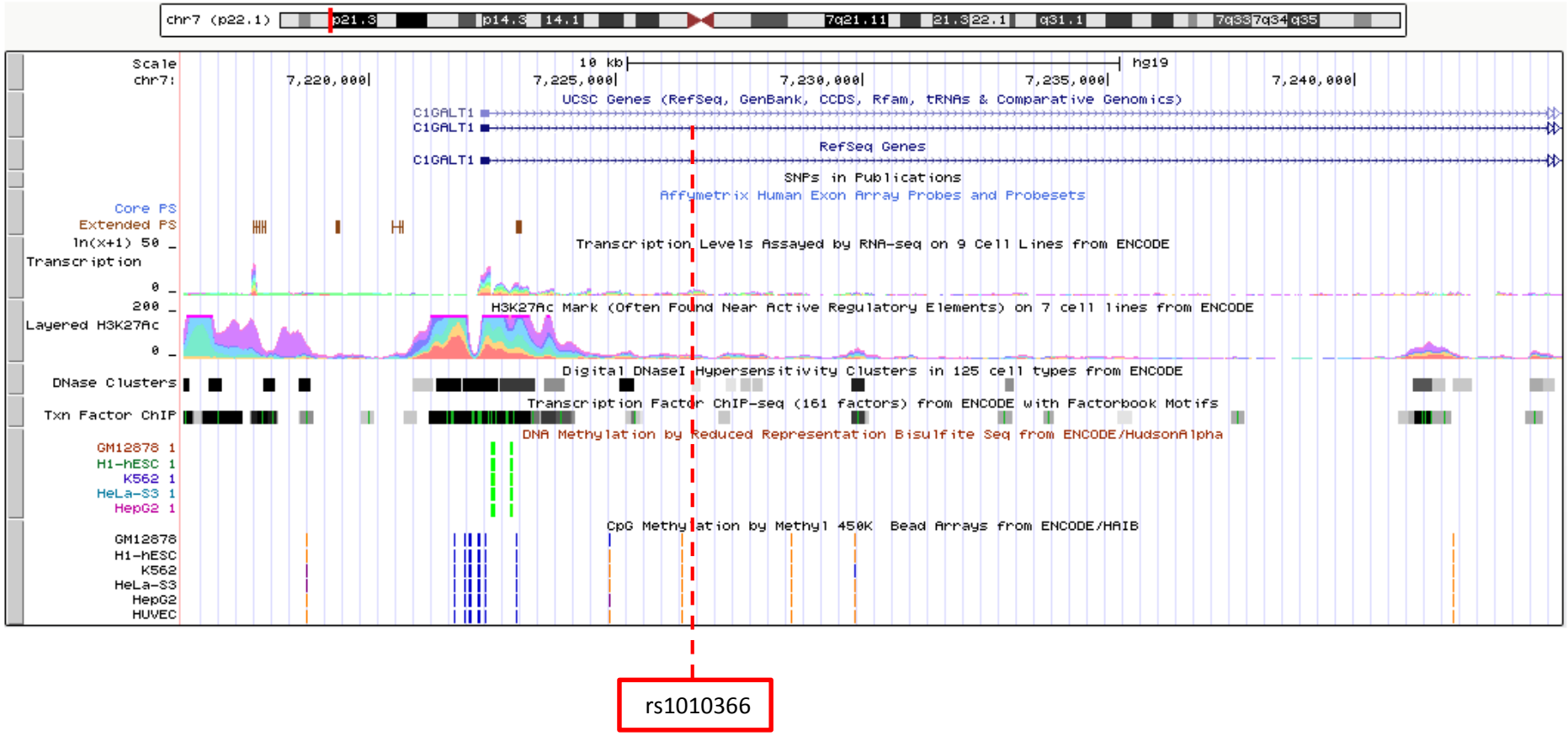
(A)


chr15 (q23)
Scale
chr15:
68,600,000
50 kb
hg19
68,650,000
68,700,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
FEM1B
ITGA11
RefSeq Genes
SNPs in Publications
1 articles
Affymetrix Human Exon Array Probes and Probesets
Core PS
Extended PS
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
DNA Methylation by Reduced Representation Bisulfite Seq from ENCODE/HudsonAlpha
GM12878 1
H1-hESC 1
K562 1
HeLa-S3 1
HepG2 1
CpG Methylation by Methyl 450K Bead Arrays from ENCODE/HAIB
GM12878
H1-hESC
K562
HeLa-S3
HepG2
HUVEC
rs1563894

(B)

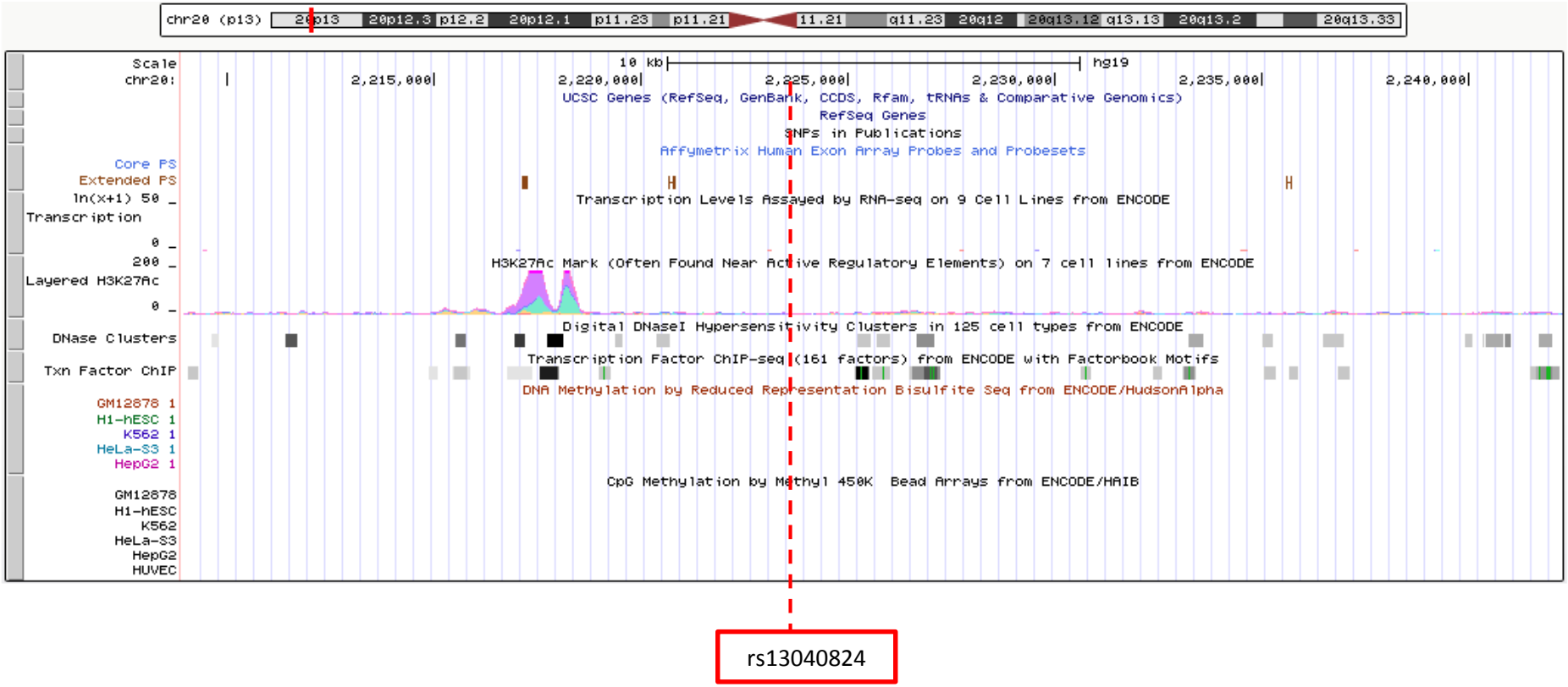

chr9 (p24.2)
9p23
p21.3
21.1
12
9q12
13
q31.1
32
33.1
33.3
Scale
chr9:
100 kb
hg19
2,450,000
2,500,000
2,550,000
2,600,000
2,650,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
FLJ35024
FLJ35024
FLJ35024
VLDLR
VLDLR
VLDLR
RefSeq Genes
VLDLR-AS1
VLDLR
VLDLR
SNPs in Publications
1 articles
1 articles
1 articles
Affymetrix Human Exon Array Probes and Probesets
Core PS
Extended PS
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
0
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
DNA Methylation by Reduced Representation Bisulfite Seq from ENCODE/HudsonAlpha
GM12878 1
H1-hESC 1
K562 1
HeLa-S3 1
HepG2 1
CpG Methylation by Methyl 450K Bead Arrays from ENCODE/HAIB
GM12878
H1-hESC
K562
HeLa-S3
HepG2
HUVEC
rs872256

(C)



Supplementary Figure 19: An overview of the ENCODE functional activity of SNPs significantly most associated with SBP across each epoch (transcriptional active region, H3K27Ac active regulatory elements, DNase hypersensitivity transcription factor binding site information from chromatin immunoprecipitation (ChIP) analysis and CpG methylation levels) (corresponding with Table 2). (A) rs1513894 (pre-puberty), (B) rs872256 (puberty) and rs1010366 (post-puberty).

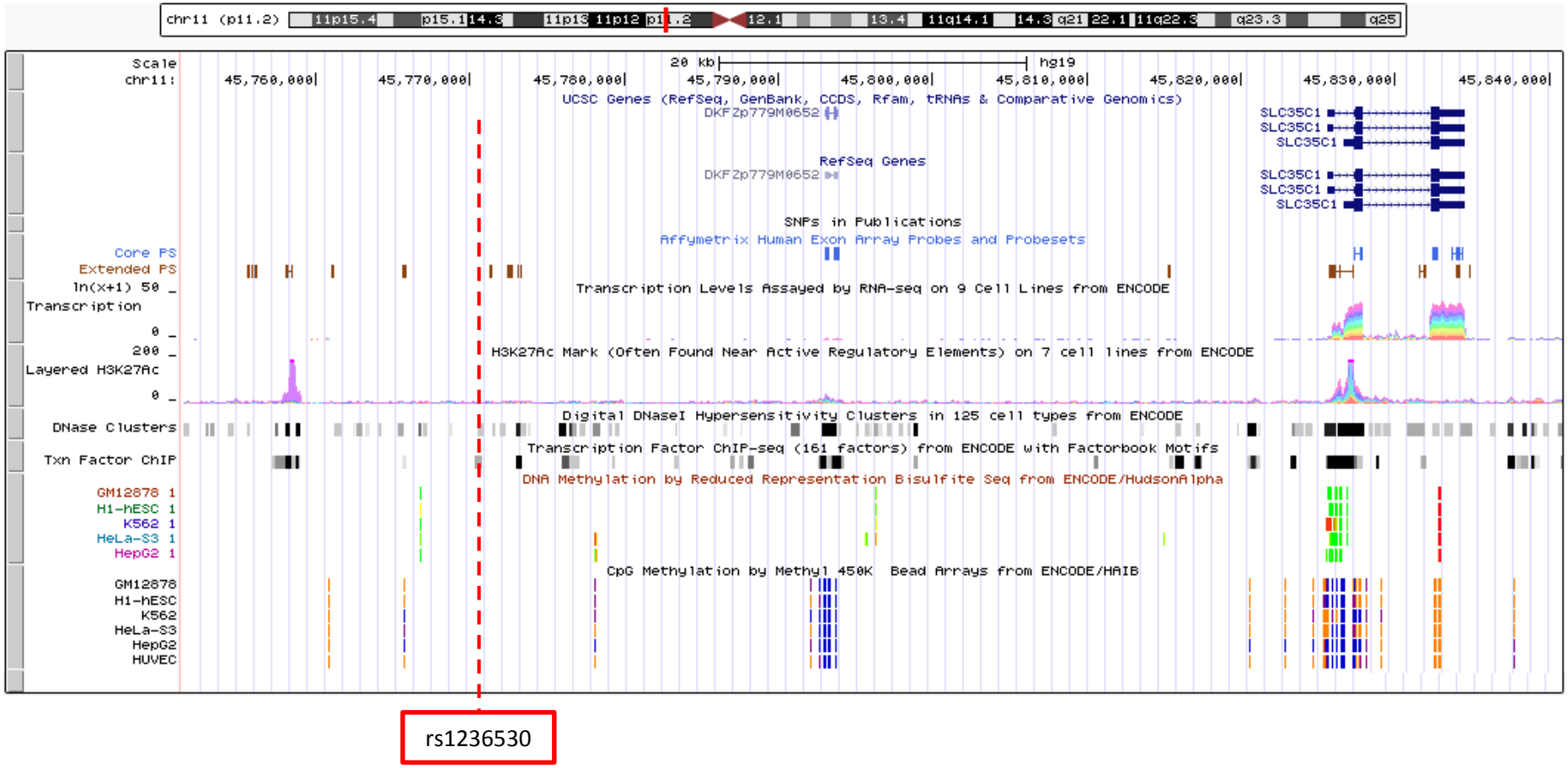
(A)


chr20 (p13)
Scale
chr20:
10 kb
hg19
2,215,000
2,220,000
2,225,000
2,230,000
2,235,000
2,240,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
RefSeq Genes
SNPs in Publications
Affymetrix Human Exon Array Probes and Probesets
Core PS
Extended PS
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
0
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
DNA Methylation by Reduced Representation Bisulfite Seq from ENCODE/HudsonAlpha
GM12878 1
H1-hESC 1
K562 1
HeLa-S3 1
HepG2 1
CpG Methylation by Methyl 450K Bead Arrays from ENCODE/HAIB
GM12878
H1-hESC
K562
HeLa-S3
HepG2
HUVEC
rs13040824

(B)

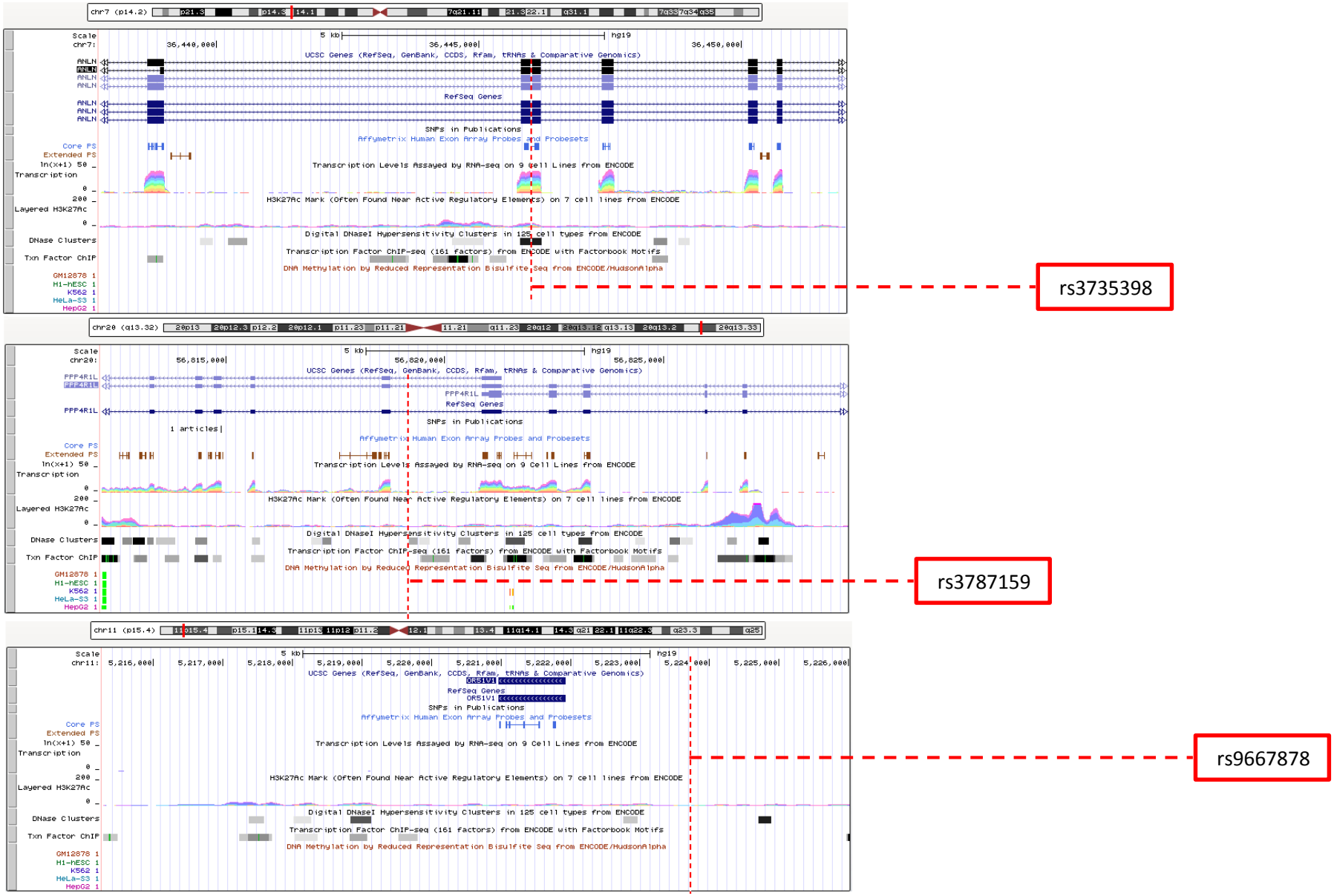

chr10 (q26.13)
10p14 p13
12.1
10q21.1
q21.3
q23.1
q25.1
25.3
26.3
Scale
chr10:
200 kb
hg19
125,700,000
125,750,000
125,800,000
125,850,000
125,900,000
125,950,000
126,000,000
126,050,000
126,100,000
126,150,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
CPXM2
CHST15
OAT
LHPP
NKX1-2
RefSeq Genes
SNPs in Publications
1 articles
Affymetrix Human Exon Array Probes and Probesets
Core PS
Extended PS
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
DNA Methylation by Reduced Representation Bisulfite Seq from ENCODE/HudsonAlpha
GM12878 1
H1-hESC 1
K562 1
HeLa-S3 1
HepG2 1
CpG Methylation by Methyl 450K Bead Arrays from ENCODE/HAIB
GM12878
H1-hESC
K562
HeLa-S3
HepG2
HUVEC
rs7897969

(C)



Supplementary Figure 20: An overview of the ENCODE functional activity of SNPs significantly most associated with DBP across each epoch (transcriptional active region, H3K27Ac active regulatory elements, DNase hypersensitivity , transcription factor binding site information from chromatin immunoprecipitation (ChIP) analysis and CpG methylation levels) (corresponding with Table 2). (A) rs13040824 (pre-puberty), (B) rs7897969 (puberty) and rs12365302 (post-puberty).

(B)


chr7 (p14.2)
Scale
chr7:
36,440,000
5 kb
hg19
36,445,000
36,450,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
ANLN
RefSeq Genes
SNPs in Publications
Affymetrix Human Exon Array Probes and Probesets
Core PS
Extended PS
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
DNA Methylation by Reduced Representation Bisulfite Seq from ENCODE/HudsonAlpha
GM12878 1
H1-hESC 1
K562 1
HeLa-S3 1
HepG2 1
rs3735398
chr20 (q13.32)
Scale
chr20:
56,815,000
5 kb
hg19
56,820,000
56,825,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
PPP4R1L
RefSeq Genes
SNPs in Publications
1 articles
Affymetrix Human Exon Array Probes and Probesets
Core PS
Extended PS
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
DNA Methylation by Reduced Representation Bisulfite Seq from ENCODE/HudsonAlpha
GM12878 1
H1-hESC 1
K562 1
HeLa-S3 1
HepG2 1
rs3787159
chr11 (p15.4)
Scale
chr11:
5,216,000
5,217,000
5,218,000
5 kb
hg19
5,219,000
5,220,000
5,221,000
5,222,000
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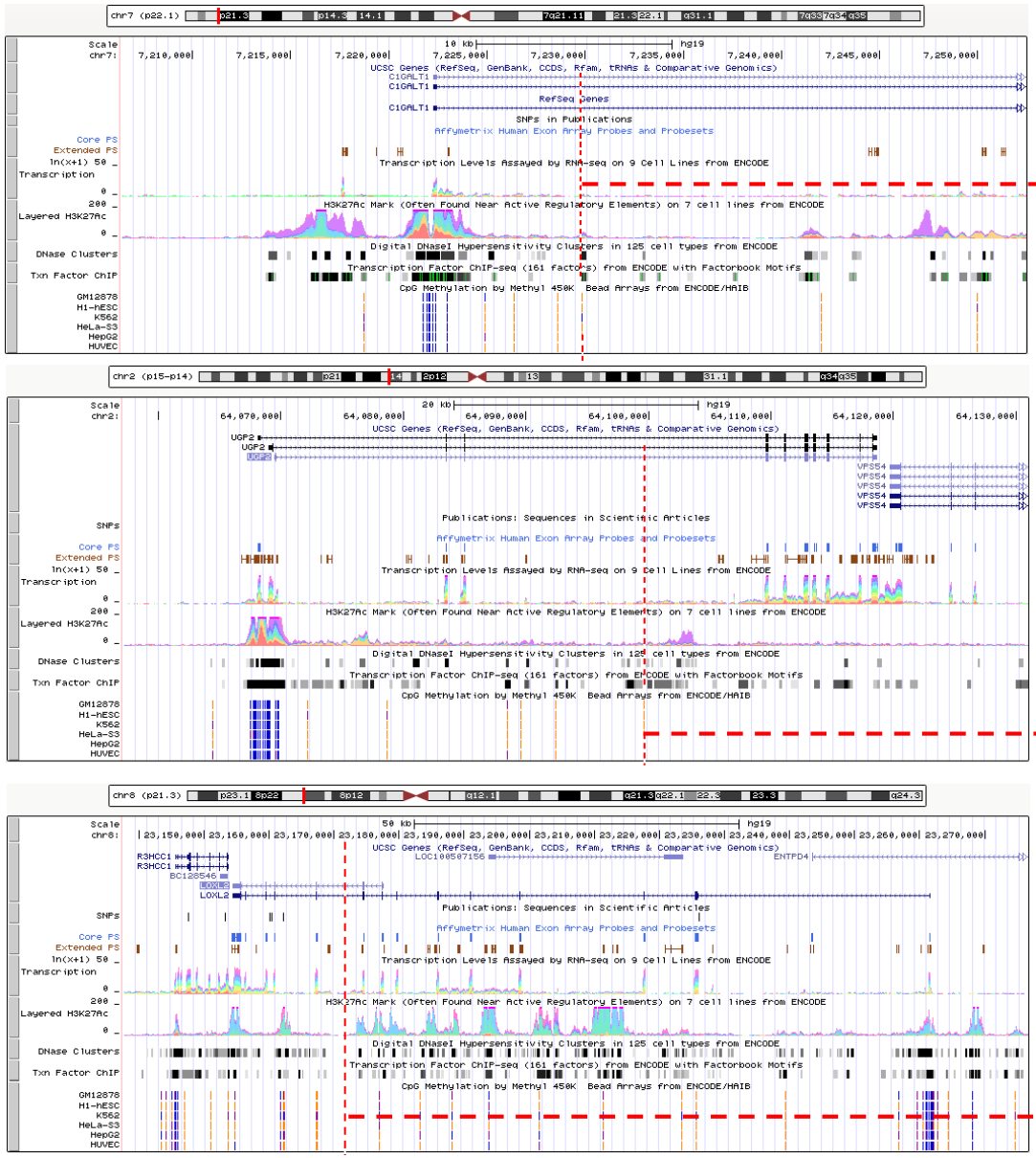
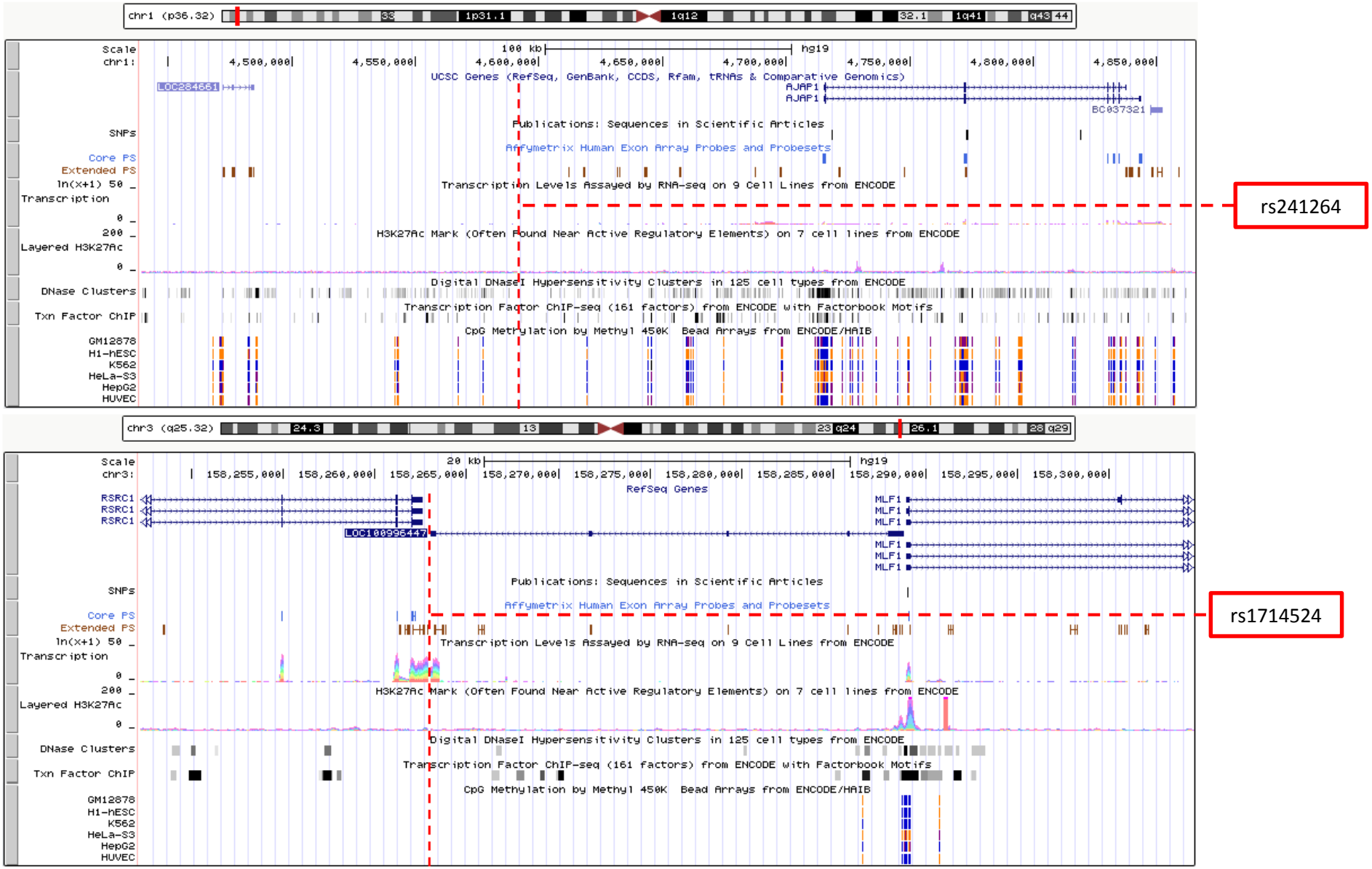
5,224,000
5,225,000
5,226,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
OR51V1
RefSeq Genes
SNPs in Publications
Affymetrix Human Exon Array Probes and Probesets
Core PS
Extended PS
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
DNA Methylation by Reduced Representation Bisulfite Seq from ENCODE/HudsonAlpha
GM12878 1
H1-hESC 1
K562 1
HeLa-S3 1
HepG2 1
rs9667878

(C)


chr7 (p22.1)
Scale
chr7:
7,210,000
7,215,000
7,220,000
7,225,000
7,230,000
7,235,000
7,240,000
7,245,000
7,250,000
10 kb
hg19
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
C1GALT1
RefSeq Genes
SNPs in Publications
Affymetrix Human Exon Array Probes and Probesets
Core PS
Extended PS
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
CpG Methylation by Methyl 450K Bead Arrays from ENCODE/HAIB
GM12878
H1-hESC
K562
HeLa-S3
HepG2
HUVEC
rs1010366
chr2 (p15-p14)
chr2:
64,070,000
64,080,000
64,090,000
64,100,000
64,110,000
64,120,000
64,130,000
20 kb
UGP2
VPS54
Publications: Sequences in Scientific Articles
rs4538187
chr8 (p21.3)
chr8:
23,150,000
23,160,000
23,170,000
23,180,000
23,190,000
23,200,000
23,210,000
23,220,000
23,230,000
23,240,000
23,250,000
23,260,000
23,270,000
50 kb
R3HCC1
BC128546
LOXL2
LOC100507156
ENTPD4
rs3901287

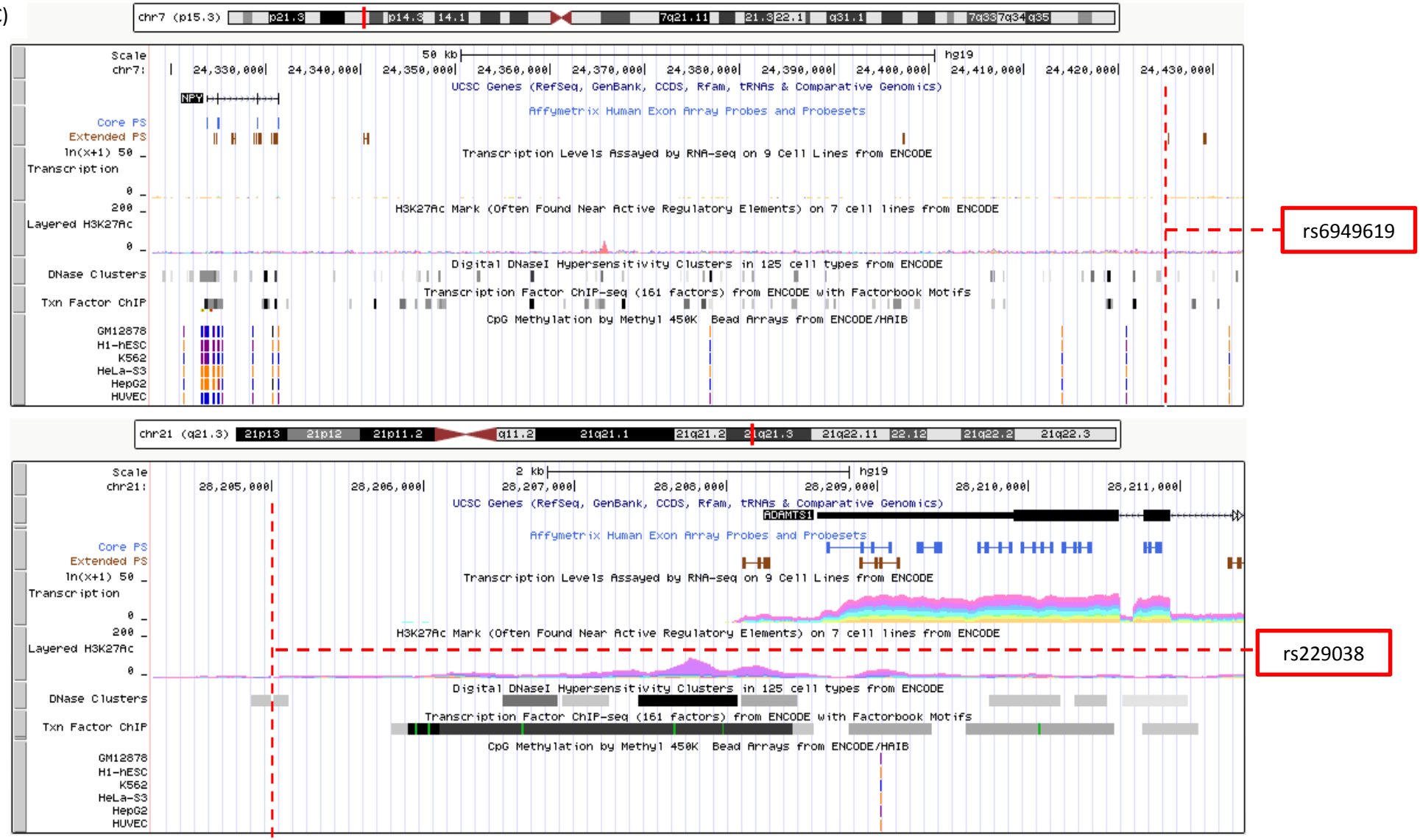
Supplementary Figure 21: An overview of the ENCODE functional activity for 'SNP clusters' significantly most associated with SBP across each epoch (transcriptional active region, H3K27Ac active regulatory elements, DNase hypersensitivity transcription factor binding site information from chromatin immunoprecipitation (ChIP) analysis and CpG methylation levels) (corresponding with Table 3). (A) rs1513894 (pre-puberty) not shown – see Supplementary Figure 19(A), (B) rs3735398, rs3787159 and rs9667878 (puberty) and rs1010366, rs4538187 and rs3901287 (post-puberty).

(A)


chr1 (p36.32)
Scale
chr1:
100 kb
hg19
4,500,000
4,550,000
4,600,000
4,650,000
4,700,000
4,750,000
4,800,000
4,850,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
LOC284661
AJAP1
AJAP1
BC037321
SNPs
Publications: Sequences in Scientific Articles
Core PS
Extended PS
Affymetrix Human Exon Array Probes and Probesets
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
0
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
CpG Methylation by Methyl 450K Bead Arrays from ENCODE/HAIB
GM12878
H1-hESC
K562
HeLa-S3
HepG2
HUVEC
rs241264
chr3 (q25.32)
Scale
chr3:
20 kb
hg19
158,255,000
158,260,000
158,265,000
158,270,000
158,275,000
158,280,000
158,285,000
158,290,000
158,295,000
158,300,000
RefSeq Genes
RSRC1
RSRC1
RSRC1
LOC100996447
MLF1
MLF1
MLF1
MLF1
MLF1
MLF1
SNPs
Publications: Sequences in Scientific Articles
Core PS
Extended PS
Affymetrix Human Exon Array Probes and Probesets
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
0
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
CpG Methylation by Methyl 450K Bead Arrays from ENCODE/HAIB
GM12878
H1-hESC
K562
HeLa-S3
HepG2
HUVEC
rs1714524

(B)

(C)


chr7 (p15.3)
Scale
chr7:
50 kb
hg19
24,330,000
24,340,000
24,350,000
24,360,000
24,370,000
24,380,000
24,390,000
24,400,000
24,410,000
24,420,000
24,430,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
NPY
Affymetrix Human Exon Array Probes and Probesets
Core PS
Extended PS
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
0
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
CpG Methylation by Methyl 450K Bead Arrays from ENCODE/HAIB
GM12878
H1-hESC
K562
HeLa-S3
HepG2
HUVEC
rs6949619
chr21 (q21.3)
Scale
chr21:
2 kb
hg19
28,205,000
28,206,000
28,207,000
28,208,000
28,209,000
28,210,000
28,211,000
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
ADAMTS1
Affymetrix Human Exon Array Probes and Probesets
Core PS
Extended PS
ln(x+1) 50
Transcription
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
0
200
Layered H3K27Ac
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
0
DNase Clusters
Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs
CpG Methylation by Methyl 450K Bead Arrays from ENCODE/HAIB
GM12878
H1-hESC
K562
HeLa-S3
HepG2
HUVEC
rs229038

Supplementary Figure 22: An overview of the ENCODE functional activity for 'SNP clusters' significantly most associated with DBP across each epoch (transcriptional active region, H3K27Ac active regulatory elements, DNase hypersensitivity transcription factor binding site information from chromatin immunoprecipitation (ChIP) analysis and CpG methylation levels) (corresponding with Table 3). (A rs241264 and rs1714524 (pre-puberty), (B) rs16875222, rs12237240 and rs1387977 (puberty) and rs6949619 and rs229038 (post-puberty).

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Analyses

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Meta-analyses of GWAS

Priyakumari G. Parmar[1], H.Rob. Taal[2, 3]

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