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ORIGINAL RESEARCH

Genetic Variants Associated With Systolic Blood Pressure in Children and Adolescents

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BACKGROUND: Genetics, along with lifestyle and behavioral characteristics, play an important role in hypertension in adults. Our aim was to identify genetic variants associated with blood pressure in childhood and adolescence.

METHODS AND RESULTS: We conducted a candidate single-nucleotide polymorphism (SNP) analysis and genome-wide association study among 9778 participants aged <18 years in BioVU, the Vanderbilt University Medical Center biobank. The outcome was childhood blood pressure percentile from age 0 to 18 years. For the candidate SNP analysis, a total of 457 previously identified SNPs were examined. Linear regression was used to test the association between genetic variants and median systolic blood pressure (SBP) percentile. Adjusted models included median age, self-reported sex, race, the first 4 principal components of ancestry, and median body mass index *Z* score. Analyses were conducted in the overall cohort and stratified by age group. A polygenic risk score was calculated for each participant, and the association between polygenic risk score and median SBP percentile in childhood was examined using linear regression. In the overall candidate SNP analysis, 2 SNPs reached significance: *rs1018148* (*FBN1*; $P=1.0\times10^{-4}$) and *rs11105354* (*ATP2B1*; $P=1.4\times10^{-4}$). In the postpuberty age group, 1 SNP reached significance: *rs1018148* (*FBN1*; $P=2.2\times10^{-5}$). In the genome-wide association study of all participants, no SNPs reached genome-wide significance. Higher polygenic risk score was associated with higher SBP percentile (β, 0.35 [95% CI, 0.10–0.60)], and there was a significant interaction with age (*P* for interaction<0.01).

CONCLUSIONS: These findings suggest that genetic variants play an important role in SBP in childhood and adolescence and provide evidence for age-specific genetic associations with SBP.

Key Words: childhood ■ genome-wide association study ■ single-nucleotide polymorphism ■ systolic blood pressure

In the United States in 2016, 13.3% of children aged 8 to 17 years had elevated blood pressure and 4.9% had hypertension, according to the American Academy of Pediatrics.[1] Genetic variation, along with lifestyle and behavioral characteristics, plays an important role in hypertension among adults. Between 2% and 3% of the variation in hypertension is explained by known common genetic variants.[2] Major progress has been made in finding genetic variants for blood pressure and hypertension in adults, but minimal evidence exists for early age or age-specific genetic associations.

Previous studies have explored whether genetic variants associated with blood pressure among adults were also associated with blood pressure in children and adolescents by using adult-based genetic risk scores. Although these genetic risk scores were associated with blood pressure in children, the studies additionally showed that the scores explained less variance in childhood blood pressure than in adult blood pressure. Recent evidence suggests that blood pressure levels change with age and that a possible interaction between age and genetic variants exists.[3,4]

To date, only one genome-wide association study (GWAS) of blood pressure has been conducted in individuals aged <18 years, where 2 novel genetic variants were identified: *rs1563894* in gene *ITGA11* during

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CLINICAL PERSPECTIVE

What Is New?

- Among a population of children aged <18 years with existing genotype data, we identified 2 single-nucleotide polymorphisms associated with systolic blood pressure percentile measured during childhood that were previously associated with adulthood systolic blood pressure.
- A multiancestry adult-based polygenic risk score was associated with systolic blood pressure percentile in childhood, and the association changed with age.

What Are the Clinical Implications?

- These findings serve as a comparison for genetic variants already identified in children, adolescents, and adults, and they provide evidence for age-specific genetic associations with blood pressure.
- Understanding blood pressure during early life is important to reduce cardiovascular consequences in adulthood.

Nonstandard Abbreviations and Acronyms

PRS	polygenic risk score
SBP	systolic blood pressure
VUMC	Vanderbilt University Medical Center

prepuberty and *rs872256* in gene *VLDLR-AS1* during puberty.[5] Although this study provides evidence for age-specific genetic associations, the study was limited by power and was restricted to individuals of European ancestry.

To investigate whether genetic variants associated with systolic blood pressure (SBP) in adulthood are associated with blood pressure in children, we conducted a candidate single-nucleotide polymorphism (SNP) analysis and GWAS in participants from Vanderbilt University Medical Center's (VUMC's) DNA repository, BioVU. We stratified analyses by age to examine the interaction between age and genetic variants. We additionally investigated the performance of a multiancestry adult-based polygenic risk score (PRS) on blood pressure among children.

METHODS

Requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to VUMC BioVU Team at biovu@vumc.org. The summary GWAS data can be accessed by request to the corresponding author and will be available at the GWAS Catalog (https://www.ebi.ac.uk/gwas/).

Study Population and Design

We conducted a candidate SNP analysis and GWAS among non-Hispanic White and Black participants in BioVU, the VUMC biobank of DNA from discarded blood collected during routine clinical testing and linked to deidentified electronic medical records. BioVU as a resource, including its ethical, privacy, and other protection, has been described previously.[6,7] We included individuals aged <18 years with genotype data available and with 2 outpatient blood pressure measurements on different days in the medical record. Our study included 9778 participants. The study was approved by the Institutional Review Board of VUMC, and informed consent was waived, as all patients consented to participate in BioVU at the time of consent to treatment.

Genotyping and Imputation

SNPs were genotyped on the Illumina Infinium Expanded Multi-Ethnic Genotyping Array chip (Illumina Inc, San Diego, CA), which contains >2 million SNPs and covers 65.7% of GWAS catalog SNPs. Imputation with reference to the 1000 Genomes phase 3 was performed using the Michigan Imputation Server.[8] SNPs with minor allele frequency <0.05 or Hardy-Weinberg equilibrium $P<10^{-6}$ were excluded.

Statistical Analysis

The outcome of interest was childhood and adolescent blood pressure percentile. All blood pressure measurements were restricted to outpatient visits. Median SBP percentile was estimated for each participant from age 0 to 18 years, using the 2017 American Academy of Pediatrics Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents, based on age, sex, and height.[9] We selected for replication (candidate SNP analysis) 457 SNPs previously reported to be associated with SBP from 3 large GWASs in adults and 2 SNPs previously identified in a GWAS on childhood and adolescent blood pressure, *rs1563894* and *rs872256*.[5,10–12]

Linear regression was used to test the association between genetic variants and median SBP percentile. Adjusted models included median age, self-reported sex, race, the first 4 principal components of ancestry, and median body mass index (BMI) *Z* score. BMI *Z* score was created from the World Health Organization Child Growth Charts based on age and sex.[13] SNPs were examined under an additive model as 0, 1, or 2

minor alleles. Analyses were stratified by race and then meta-analyzed using METAL.[14]

Analyses were additionally stratified by age group: 0 to 3, 4 to 7, 8 to 12, and 13 to 18 years. For these analyses, median SBP percentile was created for each participant within the given age group. Participants could contribute to >1 age group if blood pressure measurements were present at multiple ages within an individual. Linear regression was used to test the association between genetic variants and median SBP percentile in each age group. Adjusted models included self-reported sex, race, the first 4 principal components of ancestry, and median BMI *Z* score for each participant during the time he or she qualified for the age group. Age-stratified analyses were stratified by race and meta-analyzed using METAL.[14]

A GWAS was also conducted to examine the association between all available SNPs and median SBP percentile. Analyses were conducted in the overall participant group (ages 0–18 years) and stratified by age group. All analyses were initially stratified by race and meta-analyzed. Adjusted models included median age (for overall analysis only), self-reported sex, race, the first 4 principal components of ancestry, and median BMI *Z* score. The interaction between age and each SNP was also examined in additive models in which median SBP percentile was regressed against each SNP, including a multiplicative interaction term between median age and each SNP, and adjusting for self-reported sex, race, the first 4 principal components of ancestry, and median BMI *Z* score.

To adjust for multiple comparisons in the candidate SNP analysis, q values were calculated using the Benjamini-Hochberg procedure, and a false discovery rate $P<0.05$ was considered significant.[15] A P of 5×10^{-8} was considered significant for the GWAS, and $P<5\times10^{-6}$ was deemed borderline significant. PLINK 1.9 was used for all genetic analyses, and R version 3.6.2 was used to produce all Manhattan and quantile-quantile plots.[16,17]

PRS Analysis

A PRS was calculated for each participant from imputed genetic data using a multiancestry score for SBP in adults, using PRS-CS (Polygenic Risk Score-Continuous Shrinkage).[18] The association between PRS and median SBP percentile in childhood was examined using linear regression. Adjusted analyses included median age, sex, race, median BMI *Z* score, and the first 4 principal components of ancestry. A second adjusted model additionally included childhood hypertension medication use and childhood presence of diabetes. Childhood diabetes was defined as use of a diabetes medication for those aged <18 years or the presence of an *International Classification of Diseases, Tenth Revision* (*ICD-10*), diagnosis code for diabetes (E08–E13) for those aged <18 years. We also examined the interaction between median age and PRS using a likelihood ratio test by including a multiplicative *age*PRS* interaction term in the model. Analyses were stratified by age group. In participants with available blood pressure measurements aged >18 years, we additionally examined the association between PRS for each participant and adulthood median SBP. Adjusted analyses included median age, race, sex, and the first 4 principal components of ancestry. A $P=0.05$ was considered statistically significant. PGS Calculator was used to calculate PRS for each participant.[19] Association analyses were conducted in Stata 16.[20]

Table 1. Participant Characteristics of Children Aged <18 Years With Genetic Data Available

Characteristic	Value (N=9778)
Age, y	11 (5 to 15)
Race	
White	7393 (75.6)
Black	2385 (24.4)
Sex	
Male	4488 (45.9)
Female	5290 (54.1)
Body mass index *Z* score	0.62 (−0.24 to 1.69)
Age group, y	
0–3	2881
4–7	3174
8–12	4294
13–18	5139
Hypertension medication	1095 (11.2)
Diabetes medication	301 (3.1)
Systolic blood pressure percentile	84.5 (66.5 to 94)
Polygenic risk score	−1.95 (−3.05, 0.09)

Values are listed as number, number (percentage), or median (interquartile range); participants can belong to >1 age group.

RESULTS

The median (interquartile range) age of participants aged 0 to 18 years was 11 (5–15) years. Most participants were White participants (75.6%) and female (54.1%). A total of 11% were on hypertension medications in childhood, and 3% had diabetes during childhood. The median (interquartile range) SBP percentile during childhood was the 84.5 (66.5–94) percentile. In the age-stratified groups, there were 2881, 3174, 4294, and 5139 participants in the 0 to 3, 4 to 7, 8 to 12, and 13 to 18 years age groups, respectively (Table 1).

In the candidate SNP analysis for the overall group of participants, 2 SNPs reached significance based on

Table 2. Top 5 Independent Associations Between Candidate SNPs and Median SBP Percentile, Overall and Stratified by Age Group

Nearest gene	*rs* Identifier	Chromosome	Base pairs	Effect allele	Other allele	Frequency	β Value	*P* value	FDR *P* value
Overall (n=9778)									
*FBN1**	*rs1018148*	15	48903126	*A*	*C*	0.92	2.26	1.0×10^{-4}	0.03
*ATP2B1**	*rs11105354*	12	90026523	*A*	*G*	0.84	−1.52	1.4×10^{-4}	0.03
SYT1	*rs7963801*	12	79685226	*T*	*C*	0.66	1.00	1.9×10^{-3}	0.23
LOC105375921	*rs72688070*	8	81393697	*C*	*T*	0.78	1.10	2.2×10^{-3}	0.23
LINC02356	*rs10774624*	12	111833788	*G*	*A*	0.62	0.97	2.8×10^{-3}	0.23
Aged 0–3 y (n=2859)									
LOC107985892	*rs6731373*	2	68503044	*G*	*A*	0.68	−1.58	1.9×10^{-3}	0.77
JPH2	*rs6031431*	20	42795152	*A*	*G*	0.54	−1.36	9.5×10^{-3}	0.90
LOC105369687	*rs60691990*	12	20368269	*T*	*C*	0.72	−1.33	1.1×10^{-2}	0.90
FBN2	*rs6595838*	5	127868199	*G*	*A*	0.62	1.44	1.1×10^{-2}	0.90
ARHGAP29	*rs17396055*	1	94730954	*G*	*A*	0.72	−1.23	1.9×10^{-2}	0.90
Prepuberty: aged 4–7 y (n=3142)									
PLEKHA7	*rs414992*	11	16894090	*C*	*T*	0.87	−2.23	3.0×10^{-3}	0.71
SLC7A1	*rs9508495*	13	30146201	*C*	*T*	0.64	1.72	8.6×10^{-3}	0.71
CRK	*rs12941318*	17	1333598	*T*	*C*	0.55	1.32	1.1×10^{-2}	0.71
FRYL	*rs13141523*	4	48789269	*A*	*G*	0.59	1.30	1.2×10^{-2}	0.71
DUSP16	*rs736107*	12	12627410	*G*	*A*	0.70	1.40	1.2×10^{-2}	0.71
Puberty: aged 8–12 y (n=4283)									
SELENOKP3	*rs9401090*	6	119113317	*T*	*C*	0.75	1.61	1.1×10^{-3}	0.32
SLC39A8	*rs13107325*	4	103188709	*C*	*T*	0.94	2.96	1.5×10^{-3}	0.32
LINC01169	*rs1440371*	15	66941084	*G*	*A*	0.73	−1.42	2.7×10^{-3}	0.36
LOC107985892	*rs6731373*	2	68503044	*G*	*A*	0.68	−1.34	3.4×10^{-3}	0.36
DGKZ	*rs72910063*	11	46345134	*C*	*T*	0.90	1.85	1.5×10^{-2}	0.75
Postpuberty: aged 13–18 y (n=5133)									
*FBN1**	*rs1018148*	15	48903126	*A*	*C*	0.92	3.78	2.2×10^{-5}	9.2×10^{-3}
CYP2C19	*rs199562446*	10	96587751	*C*	*T*	0.89	2.67	5.1×10^{-4}	0.11
PTPN11	*rs11066320*	12	112906415	*A*	*G*	0.67	−1.56	1.9×10^{-3}	0.22
LINC02356	*rs10774624*	12	111833788	*G*	*A*	0.62	1.54	2.1×10^{-3}	0.22
LOC105379003	*rs3121685*	5	65662133	*C*	*T*	0.59	1.39	2.9×10^{-3}	0.25

Frequency refers to effect allele frequency; adjusted models included median age, self-reported sex, race, the first 4 principal components of ancestry, and median body mass index *Z* score.
FDR indicates false discovery rate; SBP, systolic blood pressure; and SNP, single-nucleotide polymorphism.
*SNP reaches FDR significance (FDR $P<0.05$).

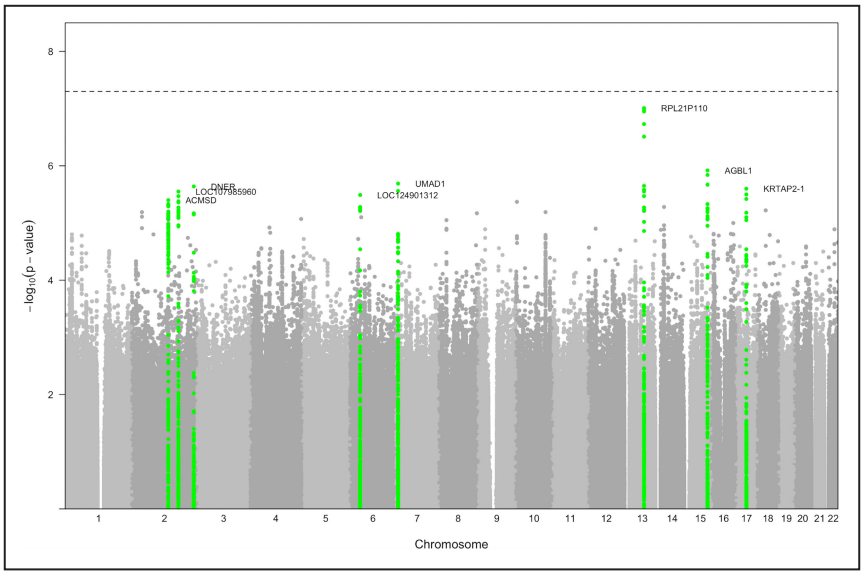

Figure 1. Manhattan plot for the genome-wide association study of all participants (N=9778).

the false discovery rate *P* value (Table 2). Every additional *A* allele at *rs1018148*, intronic in the fibrillin-1 gene (*FBN1*), was associated with 2.26 higher median SBP percentile from age 0 to 18 years (P=1.0×10^{-4}). At *rs11105354*, intronic in ATPase plasma membrane Ca^{2+} transporting 1 (*ATP2B1*), every additional *A* allele was associated with a –1.52 lower median SBP percentile from age 0 to 18 years (P=1.4×10^{-4}). In the age-stratified analyses, no SNPs reached the level of significance for SBP percentile in the 0 to 3, 4 to 7 year, or 8 to 12 years age groups. In the postpuberty age group, 13 to 18 years, 1 SNP reached significance (Table 2). The variant, *rs1018148* in gene *FBN1* (chromosome position, 15:48903126), was significantly associated with median SBP percentile from age 0 to 18 years with a β of 3.78 (P=2.2×10^{-5}). Table 2 shows the top 5 associations between the candidate SNPs and SBP percentile for each age group and in the overall population. The 2 SNPs previously associated with adolescent blood pressure, *rs1563894* and *rs872256*, were not significant in our study.

In the GWAS of all participants, no SNPs reached genome-wide significance (Figures 1 and 2). Borderline SNPs (P<5×10^{-6}) are listed in Table 3. In the age-stratified GWAS, no SNPs reached genome-wide significance (Figures 3 and 4). Table 3 shows the borderline associations between all SNPs and SBP percentile in each age group. No significant interactions

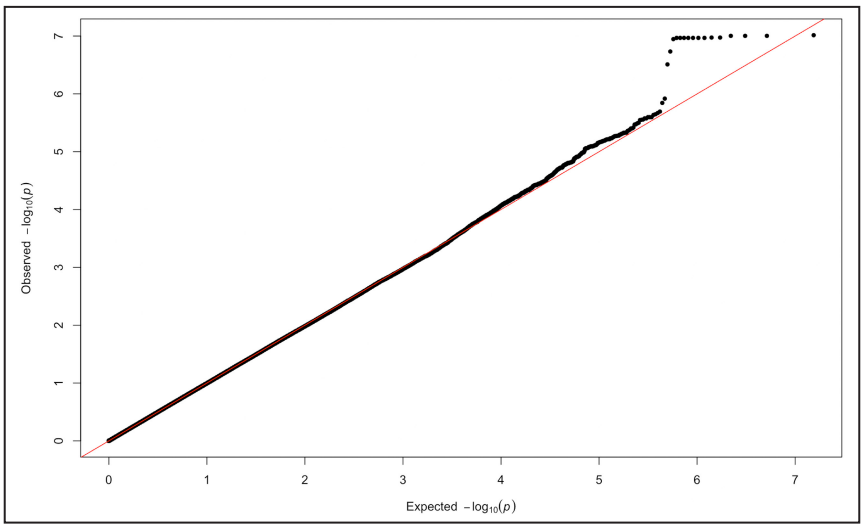

Figure 2. Quantile-quantile plot for the genome-wide association study of all participants (N=9778).

Table 3. Borderline Associations Between All SNPs and Median SBP Percentile, Overall and Stratified by Age Group

Nearest gene	*rs* Identifier	Chromosome	Base pairs	Effect allele	Other allele	Frequency	β Value	*P* value
Overall (n=9778)								
RPL21P110	*rs4119478*	13	73254212	*C*	*T*	0.67	1.65	9.7×10^{-8}
AGBL1	*rs16977994*	15	87343422	*A*	*G*	0.90	−2.39	1.2×10^{-6}
UMAD1	*rs73057784*	7	7896705	*G*	*C*	0.83	1.91	2.0×10^{-6}
DNER	*rs7576516*	2	230523831	*C*	*T*	0.63	1.43	2.3×10^{-6}
KRTAP2-1	*rs112999280*	17	39206388	*G*	*A*	0.94	−3.50	2.5×10^{-6}
LOC107985960	*rs4972502*	2	173202455	*G*	*A*	0.82	1.78	2.8×10^{-6}
LOC124901312	*rs10947677*	6	37516612	*T*	*G*	0.59	1.41	3.2×10^{-6}
ACMSD	*rs3739030*	2	135599381	*G*	*A*	0.53	−1.56	3.9×10^{-6}
Aged 0–3 y (n=2859)								
DLGAP2	*rs73549740*	8	1635301	*G*	*C*	0.93	−6.46	2.4×10^{-7}
OOEP	*rs80270200*	6	74080171	*C*	*T*	0.94	5.05	8.9×10^{-7}
TRIB1	*rs10956249*	8	126473499	*C*	*T*	0.80	2.89	9.9×10^{-7}
CEP89	*rs62125057*	19	33453527	*G*	*A*	0.94	4.81	1.5×10^{-6}
ZNF516	*rs7239053*	18	74191792	*C*	*T*	0.65	2.36	2.3×10^{-6}
DKK3	*rs11022109*	11	12024916	*G*	*A*	0.95	9.35	2.7×10^{-6}
PHACTR1	*rs1223546*	6	13162331	*T*	*C*	0.82	2.81	3.5×10^{-6}
TM4SF18	*rs9881688*	3	149043923	*T*	*A*	0.65	2.30	3.6×10^{-6}
SOGA3	*rs61743738*	6	127796867	*A*	*C*	0.95	−6.28	3.6×10^{-6}
LOC105370344	*rs1535989*	13	106022722	*A*	*G*	0.88	−3.49	3.7×10^{-6}
LOC105373716	*rs6714953*	2	160090633	*G*	*C*	0.89	−3.59	4.7×10^{-6}
Prepuberty: aged 4–7 y (n=3142)								
LOC105377428	*rs188276693*	4	133042109	*G*	*T*	0.94	5.38	1.1×10^{-7}
LOC105373831	*rs6710639*	2	199465662	*T*	*C*	0.95	−7.11	2.3×10^{-6}
LOC107986914	*rs1011158*	8	9104831	*G*	*A*	0.55	−2.71	3.2×10^{-6}
ARHGAP15	*rs2381456*	2	144184895	*A*	*G*	0.91	−3.95	3.8×10^{-6}
PLPPR1	*rs74306891*	9	103871552	*G*	*A*	0.92	6.27	4.1×10^{-6}
PPP2R2D	*rs72861371*	10	133761971	*T*	*G*	0.90	−4.23	4.6×10^{-6}
LOC124903591	*rs62025144*	15	79859443	*C*	*G*	0.92	4.71	4.7×10^{-6}
Puberty: aged 8–12 y (n=4283)								
TIMP2	*rs2005542*	17	76884226	*T*	*A*	0.90	3.37	1.4×10^{-6}
DAPP1	*rs34849574*	4	100662056	*T*	*A*	0.69	2.69	2.4×10^{-6}
LOC107987108	*rs7855801*	9	109276620	*T*	*G*	0.53	−2.32	2.6×10^{-6}
RNU6-710P	*rs76955518*	9	114771595	*G*	*A*	0.95	7.31	2.7×10^{-6}
ACACA	*rs9286331*	17	35444733	*T*	*C*	0.71	2.91	3.8×10^{-6}
SDK1	*rs77562169*	7	4283744	*C*	*A*	0.92	3.83	4.3×10^{-6}
ADAMTS9	*rs4309722*	3	64656286	*C*	*A*	0.69	2.16	4.6×10^{-6}
CLDN16	*rs62278659*	3	189975841	*T*	*C*	0.92	−3.99	4.9×10^{-6}
Postpuberty: aged 13–18 y (n=5133)								
DSCAM	*rs2989339*	21	41392326	*T*	*C*	0.58	2.25	5.21×10^{-7}
HCFC2	*rs7312227*	12	104496274	*A*	*G*	0.76	−2.55	8.0×10^{-7}
SEMA3A	*rs1228863*	7	83998413	*A*	*G*	0.95	−5.36	8.9×10^{-7}
SHANK3	*rs9616945*	22	51148424	*G*	*A*	0.88	−3.54	2.3×10^{-6}
LOC105369719	*rs11050949*	12	30708253	*C*	*T*	0.66	2.22	2.6×10^{-6}
NDUFV2	*rs7243018*	18	9071523	*A*	*C*	0.58	2.09	2.6×10^{-6}
ALDH1A2-AS1	*rs2704190*	15	58371251	*T*	*C*	0.83	−2.67	3.6×10^{-6}
LOC105372064	*rs112656296*	18	33331408	*G*	*A*	0.87	−3.02	4.0×10^{-6}
FBN1	*rs1036477*	15	48914926	*A*	*G*	0.79	−3.85	4.2×10^{-6}
LOC105374902	*rs6928965*	6	6894948	*G*	*A*	0.90	−3.70	4.3×10^{-6}

Top associations were defined as $P<5\times10^{-6}$; frequency refers to effect allele frequency; adjusted models included median age, self-reported sex, race, the first 4 principal components of ancestry, and median body mass index *Z* score.

SBP indicates systolic blood pressure; and SNP, single-nucleotide polymorphism.

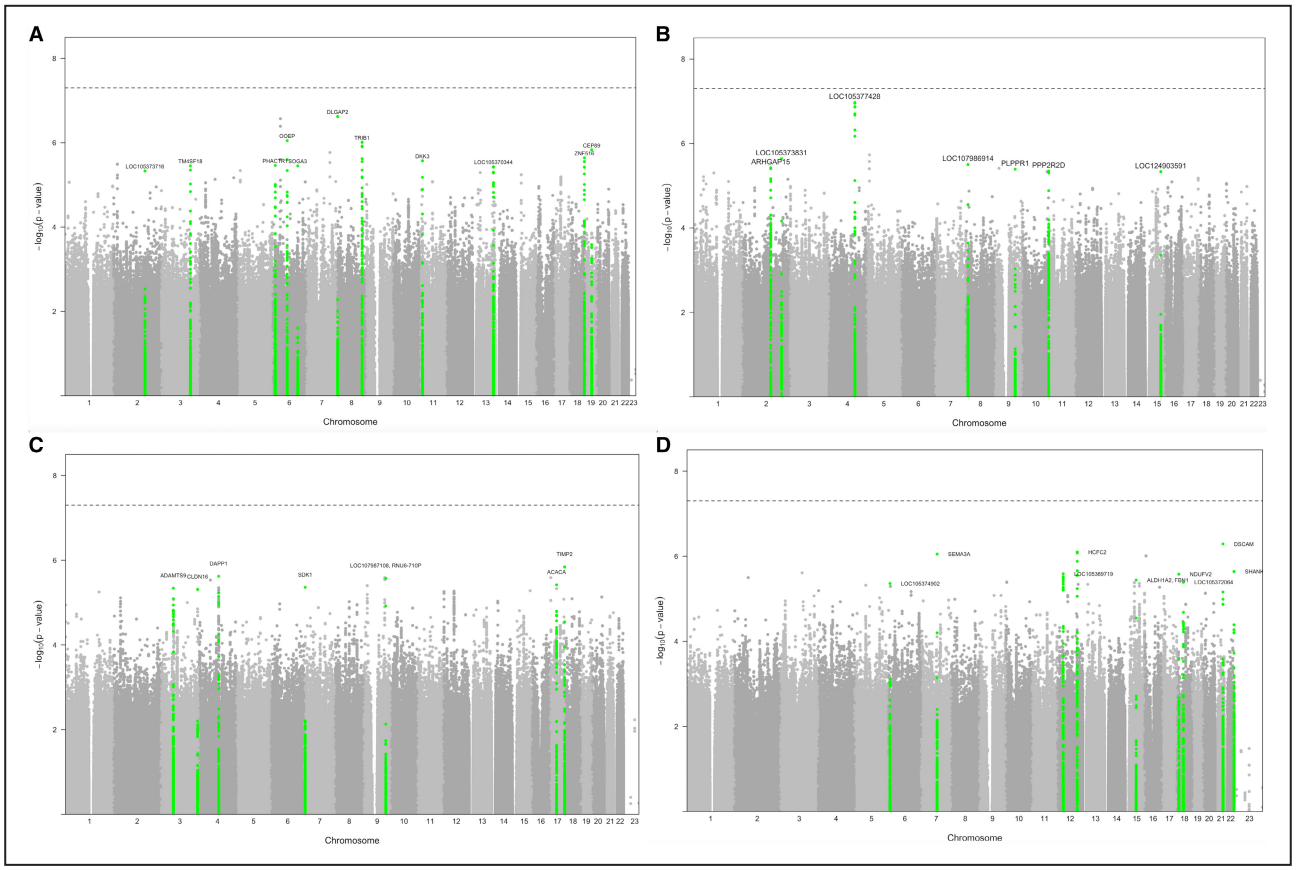

Figure 3. Manhattan plots for age-stratified genome-wide association study: 0 to 3 years (A), 4 to 7 years (B), 8 to 12 years (C), and 13 to 18 years (D).

between SNPs and age were detected (Table S1). No SNPs reached genome-wide significance in race-stratified analyses (Table S2).

In the PRS analysis, we examined the association between PRS and median SBP percentile during childhood (aged 0–18 years). After adjustment for median age, sex, race, median BMI *Z* score, the first 4 principal components of ancestry, hypertension medication, and diabetes, higher PRS was associated with higher SBP percentile (β, 0.35 [95% CI, 0.10–0.60]) (Table 4). In addition, in unadjusted analyses, a 1-unit increase in PRS was associated with a median adulthood SBP increase of 0.26 (95% CI, 0.03–0.49). This association was no longer significant after adjustment for covariates (Table S3).

The interaction term between age and PRS was significant (*P* for interaction: <0.01), with a stronger association with higher age, which is consistent with analyses stratified by age group. The association between PRS and median SBP percentile for each age group was examined (Table 4). After adjustment, there was no association between PRS and SBP percentile in the 0 to 3 and 4 to 7 years age groups. In the age group of 8 to 12 years, higher PRS was associated with higher SBP (β, 0.43 [95% CI, 0.05–0.82]). In the 13 to 18 years age group, higher PRS was associated with higher SBP (β, 0.54 [95% CI, 0.16–0.92]).

DISCUSSION

In the current study, we have identified 2 SNPs associated with SBP percentile measured during childhood that were previously associated with adulthood SBP. We originally hypothesized that genetic variants in childhood would differ from genetic variants associated with SBP in adulthood and that the genetic variants associated with SBP in children would have stronger associations because of the shorter time period for environmental influence; however, we did not find any novel genetic variants associated with SBP percentile during childhood. One genetic variant, *rs1018148* (*FBN1*), was associated with SBP percentile in the overall cohort and in the postpuberty period (aged 13–18 years). The other variant, *rs11105354* (*ATP2B1*), was associated with SBP percentile in the overall cohort. We did not find any SNPs reaching genome-wide significance with SBP percentile, overall or stratified by age group. We additionally investigated the performance of a multiancestry adult-based genetic risk

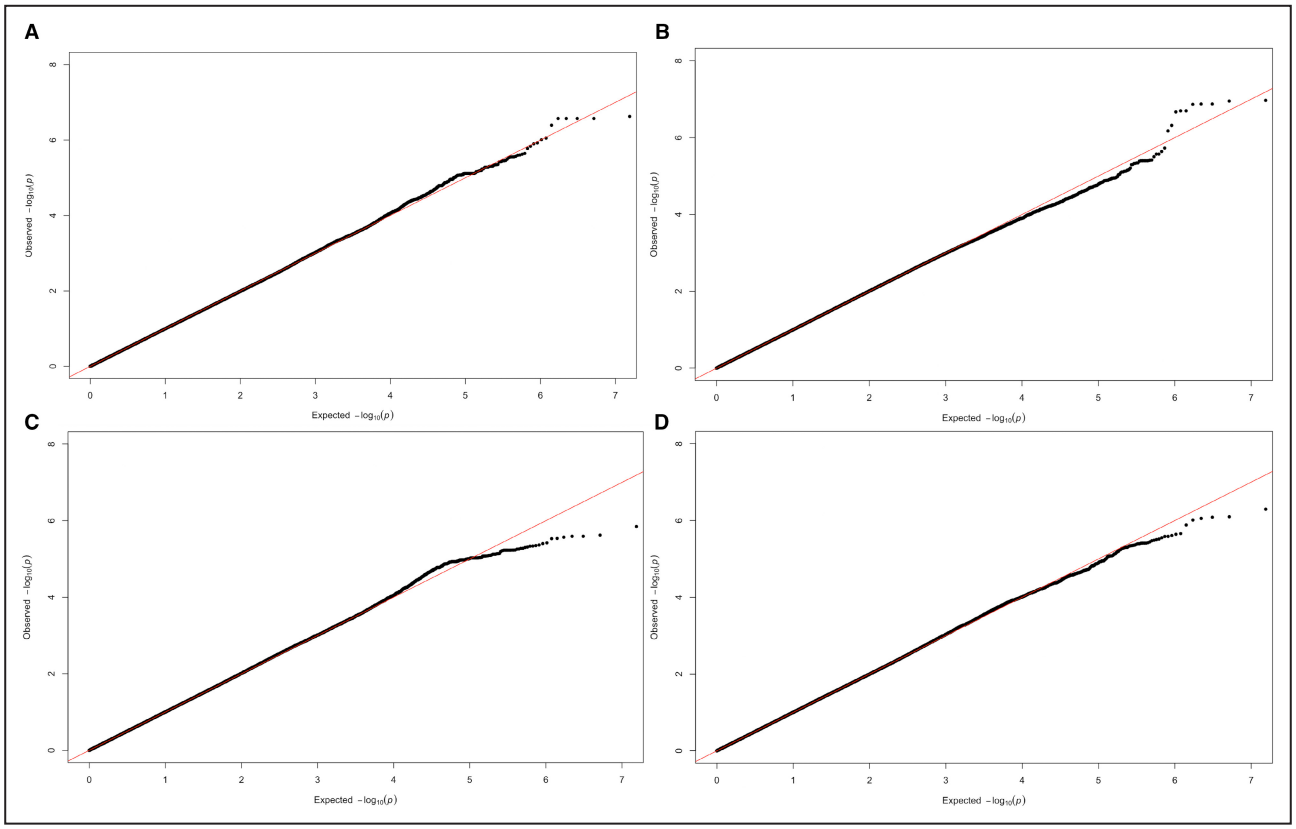

Figure 4. Quantile-quantile plots for the age-stratified genome-wide association study: 0 to 3 years (A), 4 to 7 years (B), 8 to 12 years (C), and 13 to 18 years (D).

score on SBP among children and found that PRS was associated with SBP percentile in childhood and adolescence overall and in puberty and postpuberty age groups.

One SNP, *rs1018148*, was associated with childhood SBP percentile in the overall cohort and in the postpuberty age group (aged 13–18 years) and is in the *FBN1* gene, which is a protein-coding gene. Fibrillin 1 contributes to the formation of the elastic fibers in the heart valves and the aorta during development.[21] *FBN1* has been shown to be associated with Marfan syndrome and stiff skin syndrome.[22,23] Traits associated with *FBN1* include height, BMI, aortic measurement, and systolic and diastolic blood pressure in adults.[24] An SNP in the *ATP2B1* gene was significant based on the false discovery rate *P* value in the overall cohort. *ATP2B1* is also a protein-coding gene, and the protein is responsible for primary ion transport ATPases.[25] This gene has been shown to be associated with diseases, such as nephrotic syndrome and spinocerebellar ataxia, and traits, such as pulse pressure measurement, mean arterial pressure, hypertension, coronary artery disease, and systolic and diastolic blood pressure.[26]

The current study is one of few GWASs of blood pressure in children at different ages. One other GWAS of blood pressure in children was conducted in the Early Genetics and Lifecourse Epidemiology Consortium in 23 689 participants.[5] The authors found 2 novel loci associated with SBP in prepuberty and postpuberty and reached genome-wide significance: *rs1563894* (*ITGA11*) during prepuberty and *rs872256* during puberty. In our study, these 2 SNPs were not associated with SBP in any age group in the candidate SNP analysis. The previous GWAS was conducted in only European participants, whereas our study included White and Black participants from the southeastern United States. Our sample size was also smaller compared with the Early Genetics and Lifecourse Epidemiology Consortium, which is a possible reason the findings from the previous GWAS were not replicated in our study.

An objective of the study was to examine the interaction between age and genetic variants. In preadolescent children, secondary hypertension is more common, whereas primary or essential hypertension is more common in adolescents.[27,28] Genetic variants may differ with increasing age because of this. A limitation of using electronic health record data is that we were unable to differentiate between secondary hypertension and essential hypertension. Although diagnosis codes were available, the data were not

Table 4. Association Between PRS and Median SBP Percentile in Childhood, Overall and Stratified by Age Group

	Unadjusted	Model 1	Model 2
Overall*	**0.17 (0.04 to 0.31)**	**0.38 (0.13 to 0.63)**	**0.35 (0.10 to 0.60)**
Aged 0–3 y (N=2881)	−0.23 (−0.44 to −0.01)	0.01 (−0.41 to 0.42)	0.00 (−0.42 to 0.42)
Aged 4–7 y (N=3174)	−0.06 (−0.29 to 0.16)	0.16 (−0.28 to 0.60)	0.15 (−0.29 to 0.58)
Aged 8–12 y (N=4294)	0.22 (0.02 to 0.41)	0.46 (0.08 to 0.84)	0.43 (0.05 to 0.82)
Aged 13–18 y (N=5139)	0.53 (0.33 to 0.72)	0.58 (0.20 to 0.96)	0.54 (0.16 to 0.92)

Model 1: median age (overall only), sex, race, median body mass index *Z* score, and first 4 principal components of ancestry.
Model 2: model 1+childhood hypertension medication use and childhood presence of diabetes. PRS indicates polygenic risk score; and SBP, systolic blood pressure.
Values are listed as beta (95% CI).
**P* value for interaction <0.01.

complete, and codes were inconsistent for hypertension. Children and adolescents who attend clinics regularly, and hence have more blood pressure measurements, are more likely to have elevated risk factors and increased comorbidities, including conditions that cause secondary hypertension. To mitigate this concern, we limited blood pressure measurements to those from outpatient visits. Secondary and essential hypertension may have distinct genomic determinants, and this may warrant further investigation.

Previous studies have explored whether adult genetic variants associated with blood pressure were also associated with blood pressure in children and adolescents by using adult-based genetic risk scores based on significant loci. In the first study, the association between a genetic risk score based on 13 SNPs and a single childhood measurement of blood pressure was studied in 2357 participants in the YFS (Young Finns Study).[29] The authors found that individuals with several susceptibility alleles have an average of 0.5–mm Hg higher blood pressure than those with less susceptibility alleles. These results were replicated in 1194 participants in the BHS (Bogalusa Heart Study). In another study, in the ALSPAC (Avon Longitudinal Study of Parents and Children) and the Western Australia Pregnancy Cohort, allelic scores of 29 SNPs for adult blood pressure were associated with SBP at the age of 6 years.[30] In the current study, we similarly found an association between the PRS-based SNPs associated with adulthood SBP and childhood SBP percentile. We additionally found a significant interaction between age and PRS, which suggests that blood pressure changes from childhood to adulthood.

The current study has multiple strengths. The first is the use of BioVU, VUMC's vast DNA repository, linked to the electronic health record, which provides a population of >9000 participants aged <18 years with existing genotype data. Another strength is the diverse population of participants available. Our study included White and Black participants, whereas most studies of genetic variants associated with blood pressure in children have only been conducted in European populations. We were also able to examine the interaction between genetic variants and age because repeated measures during childhood were available in the data. Our study also had several limitations. Our sample size was small and, therefore, our power to detect genome-wide associations was limited. Another limitation is that there is possible population stratification. We tried to limit this by adjusting for principal components of ancestry and stratifying by race and then meta-analyzing. Another limitation is that SBP was the only outcome and diastolic blood pressure was not included. Although data on diastolic blood pressure were available, no previous genome-wide associations of genetic variants and childhood diastolic blood pressure have been reported for use in the candidate SNP analysis.

We have identified 2 known genetic variants related to SBP in childhood, but none related to SBP overall or in any age group at genome-wide significance. We did find that a PRS created from genetic variants shown to be associated with adulthood SBP was associated with SBP percentile in childhood and that this association changed with age. These findings serve as a comparison for genetic variants already identified in children, adolescents, and adults; and they provide evidence for age-specific genetic associations with blood pressure. As this is one of few studies of genetic variants and blood pressure in children, these associations require further investigation and replication.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Top age interactions between single nucleotide polymorphisms and median systolic blood pressure percentile

Nearest Gene	rsid	Chr	Base Pair	Effect Allele	Other Allele	Freq.	Beta	p-value
Overall (n=9178)								
FSTL4	rs79477508	5	133005855	T	C	0.89	3.83	1.1×10^{-4}
	interaction						-0.48	2.7×10^{-7}
XXYLT1	rs6770150	3	194781805	G	T	0.85	-3.61	3.2×10^{-5}
	interaction						0.40	7.0×10^{-7}
F11	rs4253406	4	187191392	G	T	0.94	-5.64	1.9×10^{-5}
	interaction						0.62	8.4×10^{-7}
LOC124903205	rs61965486	13	107700149	A	T	0.82	3.98	9.5×10^{-7}
	interaction						-0.37	9.9×10^{-7}
TRIB1	rs6470355	8	126460535	A	G	0.73	-3.18	6.7×10^{-6}
	interaction						0.32	1.3×10^{-6}
OR6B2	rs7574432	2	240976327	C	T	0.77	-3.59	2.1×10^{-6}
	interaction						0.33	1.4×10^{-6}
VEPH1	rs2316336	3	157206296	T	C	0.61	2.23	4.2×10^{-4}
	interaction						-0.28	2.5×10^{-6}
KCND3	rs617531	1	112391923	A	G	0.64	-2.14	8.5×10^{-4}
	interaction						0.28	3.7×10^{-6}
LOC107984471	rs7306200	12	69524926	A	G	0.54	2.22	1.7×10^{-3}
	interaction						-0.31	3.8×10^{-6}
DCBLD1	rs9374668	6	117859198	G	A	0.89	3.16	1.4×10^{-3}
	interaction						-0.43	3.9×10^{-6}
PTPRM	rs7241594	18	7579007	T	C	0.94	-7.68	3.9×10^{-4}
	interaction						0.85	4.3×10^{-6}

Note: top associations were defined as interaction $p<5 \times 10^{-6}$; frequency refers to effect allele frequency
Abbreviations: chr, chromosome; BP, base pair; MAF, minor allele frequency; SNP, single nucleotide polymorphism; SBP, systolic blood pressure

Table S2. Borderline associations between all single nucleotide polymorphisms and median systolic blood pressure percentile, stratified by race

Nearest Gene	rsid	Chr	Base Pair	Effect Allele	Other Allele	Freq.	Beta	p-value
White Participants (n=6936)								
LINC02661	rs12780127	10	110603382	C	T	0.73	2.01	$1.7x10^{-7}$
AGBL1	rs2034633	15	87353775	A	G	0.89	-2.53	$3.0x10^{-7}$
AKAP6	rs11455295	14	32699185	A	G	0.69	1.66	$1.8x10^{-6}$
ACMSD	rs1893396	2	135599009	T	G	0.53	-1.56	$2.8x10^{-6}$
LINC02661	rs11596055	10	110478121	G	A	0.82	2.03	$2.9x10^{-6}$
AKAP6	rs7155347	14	32697558	T	C	0.70	1.61	$4.1x10^{-6}$
MAPKAPK5P1	rs2039666	10	110631824	C	T	0.60	1.63	$4.6x10^{-6}$
Black Participants (n=2242)								
MCRIP2P2	rs4651259	1	185410975	G	A	0.63	-2.77	$2.2x10^{-6}$
LOC105374920	rs370971359	6	10330362	C	T	0.89	-3.35	$2.3x10^{-6}$
KRTAP2-1	rs112999280	17	39206388	G	A	0.94	3.50	$2.5x10^{-6}$
FOXP1	rs539420592	3	71358543	A	T	0.77	-3.12	$2.5x10^{-6}$
LOC100526736	rs975967	4	86353091	A	G	0.84	-2.80	$2.6x10^{-6}$
LOC105378143	rs660011	6	169109717	C	T	0.90	-3.85	$2.6x10^{-6}$
KAZN	rs10927497	1	15004062	C	A	0.56	2.92	$2.9x10^{-6}$
LOC100526736	rs340207	4	86357577	C	T	0.72	2.81	$3.1x10^{-6}$
LOC124900344	rs4885023	13	73243986	C	T	0.69	2.69	$3.8x10^{-6}$
LINGO1	rs35119957	15	78153578	A	G	0.82	-5.76	$3.9x10^{-6}$
LINC01547	rs556954878	21	46355856	A	T	0.61	-2.61	$4.2x10^{-6}$
WNT3	rs199527	17	44843667	A	G	0.64	-2.71	$4.5x10^{-6}$
GALNT13	rs751696293	2	154729145	GGGA	G	0.62	-2.66	$4.7x10^{-6}$
SMYD3	rs6656940	1	246255826	G	A	0.81	-3.43	$4.9x10^{-6}$

Note: top associations were defined as $p<5x10^{-6}$; frequency refers to effect allele frequency
Abbreviations: chr, chromosome; BP, base pair; FDR, false discovery rate; SNP, single nucleotide polymorphism; SBP, systolic blood pressure

Table S3. Association between polygenic risk score and median systolic blood pressure in adulthood (N=877)

Unadjusted	Model 1
0.26 (0.03, 0.49)	0.24 (-0.21, 0.70)

Abbreviation: PRS, polygenic risk score
Model 1: median age, sex, race, first 4 principal components of ancestry