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Common Variants in the ATP2B1 Gene Are Associated With Susceptibility to Hypertension: The Japanese Millennium Genome Project

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ONLINE SUPPLEMENT

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The Japanese Millennium Genome Project

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SUPPLEMENTAL METHODS

ex vivo expression analysis of ATP2B1 mRNA

We obtained 34 umbilical cords at delivery (Kosei General Hospital). Umbilical arteries were excised from the cords and cut into small pieces. Umbilical artery smooth muscle cells (UASMCs) were separated using Hanks buffer containing 2 mg/ml collagenase and cultured in HuMedia-SG (Kurabo, Osaka, Japan) supplemented with epithelial growth factor (0.5 ng/ml), basic fibroblast growth factor (2 ng/ml), insulin (5 μg/ml), antibiotics and 5% fetal bovine serum. Total RNAs was extracted from UASMCs during early passages using TRIzol reagent according to manufacturer's instructions (Invitrogen, Carlsbad, CA). First-strand cDNA was synthesized from 500 ng of the total RNA using a PrimeScript 1st strand cDNA Synthesis Kit (Takara Bio, Shiga, Japan), and then diluted five times for subsequent real-time PCR (RT-PCR). RT-PCR was performed using TaqMan Gene Expression Assays on a 7900HT Sequence Detection System (Applied Biosystems). A relative quantification method [1] was used to measure the amounts of ATP2B1 (TaqMan assay ID, Hs00155949_m1) with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Hs99999905_m1) as an internal control. Genotype of ATP2B1 rs11105378 of each sample was analyzed by direct sequencing (BigDye Terminator v3.1 Cycle Sequencing Kit on a 3730xl GeneticAnalyzer, Applied Biosystems) using isolated genomic DNA from UASMCs (QIAamp DNA Mini Kit, QIAGEN GmbH, Hilden, Germany). The direct sequencing was performed with the following primers; forward 5'-TTCATAGCCCTTTTCATCTCTTTC-3', reverse 5'-AGAATCTCGGGAAAACAGCA-3'.

Table S1 Clinical characteristics of the cohort-based population sample

Parameters	Total (14,105)	Community-based general population					Company employee	
		Ohasama (1,592)	Shigaraki (2,273)	Takashima (1,730)	Suita (2,536)	Nomura (2,876)	Yokohama (2,290)	Matsuyama (808)
Age (years)	57.8±14.0	57.5±11.2	57.2±15.5	59.7±14.1	65.6±10.9	61.1±14.0	45.7±10.2	54.2±5.8
Sex (male/female)	6931/7174	601/991	862/1411	633/1097	1160/1376	1247/1629	1659/631	769/39
Body mass index (kg/m^2)	23.0±3.1	23.7±3.2	22.6±3.1	22.9±3.0	22.9±3.1	23.4±3.2	22.4±3.1	23.4±2.9
History of CVD	7.1	11.9	12.1	4.0	7.5	8.1	0.4	4.3
Systolic BP (mmHg)	130.1±19.6	131.7±14.2	130.1±19.5	130.6±21.3	124.5±18.9	137.7±22.1	123.8±14.9	134.3±19.1
Diastolic BP (mmHg)	77.9±11.5	74.4±9.4	76.7±11.7	76.8±12.0	75.6±10.5	81.0±11.8	78.3±10.3	85.1±12.2
Hypertension (%)	40.7	43.2	44.4	39.5	38.2	53.3	22.9	46.2
Antihypertensive treatment (%)	20.5	26.5	23.5	16.4	26.4	25.7	6.5	12.4

Values are mean±SD. Cardiovascular disease (CVD); stroke, myocardial infarction, and angina pectoris. Hypertension; any or all of systolic blood pressure more than 140 mmHg, diastolic blood pressure more than 90 mmHg, and current use of antihypertensive agents. The Ohasama study conducted by Tohoku University is a population-based longitudinal epidemiological study focusing on the clinical implications of home BP measurement [2]. Ohasama Town is a rural community located in the northern part of Japan (Iwate Prefecture). Subjects were recruited through a community-based annual medical check-up process. The Shigaraki [3] and Takashima [4]| studies of Shiga University of Medical Science are general population-based longitudinal studies. Both towns are located in central Japan (Shiga Prefecture). Subjects were recruited through a community-based annual medical check-up process. The Suita study conducted by the National Cardiovascular Center is based on the residents of Suita city, an urban city located in the second largest area Osaka, Japan [5]. Subjects were recruited through a biennial medical check-up process of the National Cardiovascular Center. The Nomura study of Ehime University is a longitudinal epidemiological study based on the Nomura Town residents, a largely rural community located in Ehime Prefecture [6]. Subjects were recruited through a community-based annual medical check-up process. The Yokohama (Yokohama City University) and Matsuyama (Ehime University) cohorts are derived from employees of large manufacturing industries located in Kanagawa and Matuyama City, Ehime Prefecture (western part of Japan) [7] respectively. In all cohorts, clinical parameters were obtained from personal health records during the annual or biennial medical check-up process. All study procedures were approved by the ethics committee of each University or Institution. Singed informed consent was obtained from all participating subjects.

Table S2 Clinical characteristics of the replication panel

Parameters	Hypertensive cases (1,929)	Normotensive controls (1,993)	p
Age (years)	55.1±7.1	55.2±9.5	0.680
Sex (male/female)	1,200/729	829/1,164	<0.001
Body mass index (kg/m^2)	24.4±3.1	21.9±2.7	<0.001
History of CVD (%)	5.4	0	<0.001
Systolic blood pressure (mmHg)	146.3±15.9	109.5±7.5	<0.001
Diastolic blood pressure (mmHg)	91.0±10.1	67.7±6.5	<0.001
Antihypertensive treatment (%)	47.5	0	<0.001

Values are mean±SD. Nested hypertensive cases and normotensive control subjects were chosen from the cohort-based population sample according to the following criteria: hypertensive subjects aged 64 years or younger, and were either being treated with antihypertensive medication or had a SBP more than 160 mmHg and/or DBP more than 90 mmHg; normotensive subjects aged 40 years or older, and all of SBP less than 120 mmHg, and DBP less than 80 mmHg, no current use of antihypertensive medication, and free from any history of cardiovascular disease. Cardiovascular disease (CVD) includes stroke, myocardial infarction, and angina pectoris.

Table S3 Association of 36 candidate SNPs with hypertension (replication panel)

Gene	SNP (position)	Genotype		Screening Panel					Odds ratio (p-value)			
				Genotype frequency			HWE	Call rate	Allelic	Recessive	Dominant	Additive
ACCN1	rs28933	AA/GA/GG	HT	464	974	449	0.159	97.6	1.03 (0.479)	1.07 (0.385)	1.02 (0.766)	(0.686)
			NT	469	986	485	0.466					
ADORA1	rs3766554	AA/GA/GG	HT	424	923	557	0.262	98.6	1.03 (0.548)	1.00 (0.977)	1.09 (0.289)	(0.523)
			NT	410	981	574	0.808					
ATP10A	rs3736186	GG/AG/AA	HT	791	868	263	0.312	99.4	**1.10** **(0.040)**	1.04 (0.666)	**1.18** **(0.010)**	**(0.033)**
			NT	734	963	280	0.206					
ATP10D	rs1058793	AA/GA/GG	HT	675	894	325	0.326	98.2	1.07 (0.147)	1.17 (0.060)	1.04 (0.555)	(0.169)
			NT	680	896	382	0.005					
ATP2A3	rs887387	TT/TC/CC	HT	936	775	189	0.126	98.7	1.05 (0.342)	1.02 (0.840)	1.07 (0.263)	(0.527)
			NT	936	836	200	0.508					
ATP2B1	rs2070759	GG/GT/TT	HT	582	896	399	0.118	97.2	**1.18** **(4.0*10^{-4})**	**1.2** **(0.018)**	**1.27** **(0.001)**	**(0.002)**
			NT	507	956	474	0.579					
CACNA1E	rs2293990	AA/TA/TT	HT	568	911	412	0.194	98.2	1.03 (0.532)	1.07 (0.372)	1.01 (0.881)	(0.661)
			NT	585	926	451	0.022					
CACNA2D2	rs2236957	GG/GA/AA	HT	459	925	496	0.499	97.3	1.00 (0.948)	1.00 (0.972)	1.01 (0.943)	(0.997)
			NT	471	954	512	0.523					
CAST	rs967591	AA/AG/GG	HT	442	916	552	0.100	99.1	1.00 (0.932)	0.98 (0.725)	1.02 (0.814)	(0.875)
			NT	451	964	561	0.345					
CHGA	rs3759717	CC/TC/TT	HT	744	877	288	0.263	99.1	1.00 (0.977)	0.93 (0.434)	1.04 (0.598)	(0.522)
			NT	755	943	281	0.624					
COL4A1	rs2305080	GG/GA/AA	HT	485	908	523	0.023	99.2	1.02 (0.723)	0.97 (0.707)	1.07 (0.332)	(0.468)
			NT	473	972	528	0.536					

Table S3 Continued

Gene	SNP (position)	Genotype		Screening Panel					Odds ratio (p-value)			
				Genotype frequency			HWE	Call rate	Allelic	Recessive	Dominant	Additive
DLGAP2	rs2301963	CC/CA/AA	HT	510	904	493	0.024	98.6	1.05 (0.239)	1.07 (0.368)	1.08 (0.321)	(0.516)
			NT	497	932	532	0.029					
ERCC1	rs2298881	CC/CA/AA	HT	595	899	387	0.161	97.5	1.00 (0.948)	0.96 (0.642)	1.04 (0.616)	(0.702)
			NT	600	955	388	0.821					
EXOSC3	rs7158	AA/AG/GG	HT	511	967	418	0.327	97.9	1.01 (0.850)	1.09 (0.264)	0.95 (0.452)	(0.262)
			NT	545	941	458	0.187					
FGF2	rs3747676	GG/GA/AA	HT	415	937	519	0.839	96.4	1.01 (0.892)	1.07 (0.340)	0.94 (0.424)	(0.309)
			NT	444	908	556	0.050					
GIPC1	rs3815715	GG/GA/AA	HT	734	863	309	0.040	98.8	1.03 (0.585)	0.98 (0.794)	1.07 (0.330)	(0.510)
			NT	728	927	313	0.532					
GNA14	rs1801258	TT/TC/CC	HT	317	919	675	0.888	99.0	1.05 (0.321)	1.11 (0.128)	0.90 (0.903)	(0.249)
			NT	330	899	743	0.039					
GNAI2	rs2236943	GG/GA/AA	HT	556	912	429	0.137	97.9	1.04 (0.427)	1.02 (0.751)	1.07 (0.345)	(0.640)
			NT	543	953	448	0.448					
GUCA1C	rs2715709	AA/GA/GG	HT	225	886	767	0.204	97.1	1.06 (0.242)	1.12 (0.081)	0.98 (0.824)	(0.156)
			NT	236	853	843	0.373					
HCN4	rs3743496	GG/TG/TT	HT	431	877	594	0.002	98.2	1.01 (0.859)	0.94 (0.369)	1.11 (0.192)	(0.150)
			NT	408	959	583	0.710					
HLA-DMB	rs2071556	CC/CA/AA	HT	511	932	450	0.534	98.0	1.09 (0.060)	**1.17** **(0.035)**	1.07 (0.346)	(0.105)
			NT	500	928	521	0.036					
KCNIP2	rs755381	TT/TC/CC	HT	453	904	543	0.044	98.2	1.05 (0.245)	1.03 (0.688)	1.12 (0.128)	(0.311)
			NT	425	957	569	0.548					

Table S3 Continued

Gene	SNP (position)	Genotype		Screening Panel					Odds ratio (p-value)			
				Genotype frequency			HWE	Call rate	Allelic	Recessive	Dominant	Additive
KCNMB4	rs710652	CC/AC/AA	HT	660	953	298	0.131	99.2	1.09 (0.056)	**1.28** **(0.003)**	1.03 (0.638)	**(0.012)**
			NT	669	930	379	0.083					
KCNN1	rs2278993	TT/TC/CC	HT	189	805	919	0.513	99.2	1.07 (0.152)	1.08 (0.259)	1.15 (0.207)	(0.335)
			NT	172	819	985	0.924					
PPP1R1B	rs3764352	TT/TC/CC	HT	547	940	374	0.412	96.0	1.07 (0.156)	1.16 (0.059)	1.04 (0.621)	(0.165)
			NT	546	928	431	0.333					
PTHR1	rs1138518	TT/TC/CC	HT	381	931	595	0.626	98.5	1.01 (0.814)	1.04 (0.599)	0.98 (0.843)	(0.803)
			NT	396	935	626	0.169					
PTPRT	rs3746539	AA/AG/GG	HT	495	991	430	0.119	99.1	1.04 (0.435)	1.12 (0.139)	0.99 (0.863)	(0.262)
			NT	514	975	482	0.644					
RAC2	rs929023	TT/TC/CC	HT	387	921	588	0.448	98.2	1.06 (0.200)	1.06 (0.438)	1.12 (0.173)	(0.373)
			NT	365	961	629	0.951					
RGS2	rs3767489	AA/GA/GG	HT	635	892	370	0.075	98.0	1.03 (0.483)	0.94 (0.476)	1.12 (0.099)	(0.104)
			NT	603	981	362	0.291					
RGS20	rs3816772	CC/CG/GG	HT	268	924	695	0.162	97.6	1.03 (0.543)	1.11 (0.132)	0.92 (0.377)	(0.112)
			NT	295	884	760	0.152					
SLC13A1	rs2140516	GG/GA/AA	HT	341	917	662	0.448	99.4	1.06 (0.225)	1.11 (0.135)	1.03 (0.736)	(0.322)
			NT	343	907	727	0.039					
SLC22A7	rs2270860	AA/GA/GG	HT	233	868	788	0.800	97.8	**1.1** **(0.048)**	**1.15** **(0.032)**	1.09 (0.406)	(0.100)
			NT	223	844	878	0.352					
SLC26A8	rs2295852	TT/TC/CC	HT	994	747	154	0.413	97.6	1.01 (0.835)	0.97 (0.806)	1.03 (0.690)	(0.857)
			NT	1002	779	153	0.926					

Table S3 Continued

Gene	SNP (position)	Genotype		Screening Panel					Odds ratio (p-value)			
				Genotype frequency			HWE	Call rate	Allelic	Recessive	Dominant	Additive
SLC2A11	rs2236620	AA/AG/GG	HT	308	890	715	0.266	99.0	1.04 (0.360)	1.00 (0.956)	1.16 (0.092)	(0.211)
			NT	279	953	738	0.306					
SLCO1B1	rs2291075	GG/GA/AA	HT	719	868	319	0.039	98.7	1.01 (0.866)	0.95 (0.524)	1.05 (0.466)	(0.493)
			NT	719	932	314	0.680					
WNK1	rs2255390	GG/GA/AA	HT	490	925	475	0.359	97.4	1.07 (0.139)	1.09 (0.262)	1.10 (0.201)	(0.339)
			NT	466	949	516	0.470					

The replication panel consists of 1,929 hypertensive cases and 1,993 normotensives controls selected from a 11,569 cohort sample (Table S2).

Table S4 Clinical characteristics of the screening panel

Parameters	Hypertensive cases (758)	Normotensive controls (726)
Male (n (%))	564 (74.4)	550 (75.8)
Age (years)	59.0±11.0	62.8±9.4
Body mass index (kg/m^2)	23.6±3.0	22.7±2.9
Systolic BP (mmHg)	163.5±24.6	115.9±12.0
Diastolic BP (mmHg)	100.3±15.7	72.0±7.6
Antihypertensive medication (n (%))	499 (65.8)	-

Values are mean±standard deviation. Hypertensive cases: non-obese hypertensive patients, who had a previous diagnosis of hypertension at between 30 and 59 years of age, were either being treated with antihypertensive medication or had a SBP more than 160 mmHg and/or DBP more than 100 mmHg, had a family history of hypertension in their parents and/or siblings. Normotensive controls: middle-aged to elderly subjects (aged more than 45 years), who had never been treated with antihypertensive medications, had a SBP less than 120 mmHg and DBP less than 80 mmHg, and had no family history of hypertension.

Table S5 Dense SNP analysis of the *ATP2B1* gene (screening panel)

Gene	SNP (position)	Genotype		Screening Panel					Odds ratio (p-value)			
				Genotype frequency			HWE	Call rate	Allelic	Recessive	Dominant	Additive
ATP2B1	rs3920010 (88464519)	GG/GA/AA	HT	17	191	542	0.971	97.9	0.95 (0.591)	0.72 (0.311)	0.97 (0.808)	(0.596)
			NT	22	177	504	0.187					
	rs3900133 (88512561)	CC/CA/AA	HT					NF				
			NT									
	rs1401982 (88513730)	AA/AG/GG	HT	318	328	92	0.603	96.3	1.28 (0.001)	1.34 (0.007)	1.45 (0.014)	(0.006)
			NT	249	324	118	0.474					
	rs988111 (88515650)	TT/TC/CC	HT					NF				
			NT									
	rs10858912 (88515998)	GG/GA/AA	HT					NF				
			NT									
	rs4516026 (88518251)	TT/TG/GG	HT					NF				
			NT									
	rs2854371 (88519597)	GG/GA/AA	HT	23	208	520	0.692	98.7	1.32 (0.008)	1.38 (0.333)	1.37 (0.008)	(0.028)
			NT	16	159	538	0.300					
	rs1520184 (88520698)	GG/GA/AA	HT					NF				
			NT									
	rs1356819 (88524892)	AA/AC/CC	HT	743	5	0	0.927	98.6	1.26 (0.707)	1.26 (0.706)		
			NT	709	6	0	0.910					
	rs957525 (88524946)	TT/TC/CC	HT	414	264	62	0.034	97.6	1.05 (0.554)	1.11 (0.303)	0.90 (0.599)	(0.389)
			NT	377	277	54	0.753					
	rs17017109 (88528238)	TT/TG/GG	HT	591	144	7	0.586	97.8	0.81 (0.094)	0.79 (0.079)	0.89 (0.842)	(0.211)
			NT	591	113	6	0.816					

Table S5 Continued

Gene	SNP (position)	Genotype		Screening Panel					Odds ratio (p-value)			
				Genotype frequency			HWE	Call rate	Allelic	Recessive	Dominant	Additive
ATP2B1	rs1520183 (88532742)	CC/CT/TT	HT					NF				
			NT									
	rs2681472 (88533090)	GG/GA/AA	HT	90	321	335	0.334	97.8	0.79 (0.003)	0.74 (0.044)	0.75 (0.006)	(0.012)
			NT	111	328	267	0.539					
	rs11614886 (88535251)	GG/GC/CC	HT					NF				
			NT									
	rs2070759 (88541867)	GG/GT/TT	HT	216	379	151	0.515	97.6	1.15 (0.054)	1.13 (0.297)	1.31 (0.033)	(0.096)
			NT	186	341	175	0.454					
	rs2070758 (88545352)	AA/AC/CC	HT	638	103	10	0.016	98.4	1.23 (0.113)	1.32 (0.050)	0.63 (0.377)	(0.056)
			NT	575	128	6	0.701					
	rs1050395 (88553032)	TT/TC/CC	HT	730	17	0	0.753	97.9	1.38 (0.327)	1.32 (0.406)		(0.468)
			NT	685	20	1	0.042					
	rs1050396 (88553110)	CC/CA/AA	HT					NF				
			NT									
	rs2056327 (88562685)	CC/CT/TT	HT					NF				
			NT									
	rs939329 (88564015)	AA/AG/GG	HT	196	382	168	0.485	97.4	1.08 (0.313)	1.04 (0.726)	1.18 (0.190)	(0.422)
			NT	178	343	178	0.623					
	rs7975689 (88571125)	AA/AG/GG	HT					NF				
			NT									
	rs7138016 (88572551)	TT/TA/AA	HT					NF				
			NT									

Table S5 Continued

Gene	SNP (position)	Genotype		Screening Panel					Odds ratio (p-value)			
				Genotype frequency			HWE	Call rate	Allelic	Recessive	Dominant	Additive
ATP2B1	rs12579302 (88574634)	GG/GA/AA	HT	105	310	333	0.018	98.9	0.80 (0.004)	0.76 (0.058)	0.76 (0.011)	(0.023)
			NT	127	319	273	0.046					
	rs11105359 (88575212)	TT/TG/GG	HT					NF				
			NT									
	rs11105360 (88575303)	TT/TC/CC	HT					NF				
			NT									
	rs11105361 (88576810)	CC/CA/AA	HT					NF				
			NT									
	rs7131965 (88590466)	TT/TC/CC	HT	731	15	0	0.025	98.7	0.90 (0.778)	0.83 (0.627)		(0.468)
			NT	707	11	1	0.990					
	rs11105364 (88593407)	TT/TG/GG	HT	335	322	88	0.276	97.2	1.29 (0.001)	1.36 (0.004)	1.44 (0.016)	(0.005)
			NT	261	323	113	0.295					
	rs11105368 (88598572)	GG/GC/CC	HT	349	284	89	0.883	94.0	1.25 (0.005)	1.21 (0.082)	1.53 (0.005)	(0.015)
			NT	294	260	119	0.212					
	rs7136259 (88605319)	TT/TC/CC	HT	323	325	87	0.348	97.2	1.24 (0.006)	1.22 (0.063)	1.50 (0.007)	(0.016)
			NT	277	312	119	0.389					
	rs17836871 (88606297)	TT/TC/CC	HT	419	260	61	0.025	97.8	1.08 (0.368)	1.16 (0.153)	0.90 (0.577)	(0.202)
			NT	376	282	53	0.990					
	rs11105378 (88614872)	TT/TC/CC	HT	76	301	359	0.276	97.3	0.73 ($6.3*10^{-5}$)	0.64 (0.005)	0.69 ($4.2*10^{-4}$)	($4.6*10^{-4}$)
			NT	108	320	280	0.295					
	rs12230074 (88614998)	GG/GA/AA	HT	83	328	332	0.883	97.6	0.82 (0.013)	0.70 (0.021)	0.82 (0.068)	(0.036)
			NT	108	316	282	0.212					

Table S5 Continued

Gene	SNP (position)	Genotype		Screening Panel					Odds ratio (p-value)			
				Genotype frequency			HWE	Call rate	Allelic	Recessive	Dominant	Additive
ATP2B1	rs11105379 (88619304)	TT/TC/CC	HT	450	240	39	0.348	96.3	1.11 (0.261)	1.12 (0.292)	1.16 (0.520)	(0.542)
			NT	413	244	43	0.389					
	rs10858918 (88620476)	TT/TC/CC	HT	40	266	442	0.998	98.6	0.90 (0.212)	0.82 (0.378)	0.89 (0.267)	(0.456)
			NT	46	267	402	0.852					
	rs2113894 (88623528)	AA/AT/TT	HT	459	232	43	0.063	96.3	1.12 (0.200)	1.14 (0.228)	1.17 (0.482)	(0.458)
			NT	413	235	47	0.090					
	rs1358350 (88626023)	TT/TA/AA	HT	49	202	445	<0.001	91.8	0.85 (0.085)	0.82 (0.345)	0.84 (0.113)	(0.263)
			NT	56	212	398	<0.001					
	rs12369944 (88626925)	CC/CA/AA	HT	617	97	15	<0.001	94.5	1.27 (0.066)	1.33 (0.043)	1.01 (0.976)	(0.104)
			NT	542	117	14	0.013					
	rs2280715 (88627833)	CC/CG/GG	HT	463	223	54	<0.001	97.0	1.14 (0.137)	1.16 (0.166)	1.17 (0.425)	(0.364)
			NT	413	228	59	0.001					
	rs11105381 (88630966)	GG/GA/AA	HT	452	259	37	0.990	98.2	1.09 (0.334)	1.09 (0.398)	1.18 (0.479)	(0.621)
			NT	413	255	41	0.843					
	rs1590008 (88631856)	TT/TC/CC	HT	438	265	42	0.818	98.2	1.11 (0.243)	1.12 (0.288)	1.18 (0.443)	(0.508)
			NT	399	266	47	0.767					

The screening panel is comprised of 758 middle age-onset severe hypertensive patients and 726 middle-aged to elderly evidently normotensive controls (Table S4). NF; no genotype frequency

Table S6 Association of 17 ATP2B4 SNPs with hypertension (screening panel)

Gene	SNP (position)	Genotype		Screening Panel					Odds ratio (p-value)			
				Genotype frequency			HWE	Call rate	Allelic	Recessive	Dominant	Additive
ATP2B4	rs4245719	GG/GA/AA	HT	287	343	117	0.389	98.5	0.90 (0.153)	0.90 (0.307)	0.82 (0.175)	(0.332)
			NT	293	327	94	0.854					
	rs4600103	GG/GA/AA	HT	286	312	129	0.007	94.3	1.03 (0.678)	1.08 (0.466)	0.98 (0.860)	(0.685)
			NT	252	304	117	0.128					
	rs17537593	TT/TA/AA	HT	64	237	432	<0.001	96.6	1.03 (0.704)	1.33 (0.154)	0.97 (0.761)	(0.252)
			NT	47	246	407	0.240					
	rs4951273	GG/GC/CC	HT	114	339	289	0.377	97.9	1.11 (0.178)	1.21 (0.214)	1.11 (0.323)	(0.383)
			NT	93	323	295	0.756					
	rs12749310	GG/GA/AA	HT	427	245	56	0.014	96.1	1.03 (0.766)	1.10 (0.370)	0.81 (0.305)	(0.256)
			NT	393	261	44	0.940					
	rs4297354	GG/GA/AA	HT	462	227	40	0.087	96.1	**1.20 (0.047)**	**1.27 (0.028)**	1.11 (0.662)	(0.086)
			NT	402	253	42	0.794					
	rs11576343	TT/TC/CC	HT	53	251	432	0.051	97.3	0.92 (0.323)	1.02 (0.918)	0.87 (0.202)	(0.382)
			NT	50	266	392	0.597					
	rs6594013	TT/TA/AA	HT	163	348	231	0.141	97.9	0.95 (0.443)	0.98 (0.856)	0.89 (0.310)	(0.587)
			NT	159	348	204	0.647					
	rs16852152	GG/GA/AA	HT	437	252	38	0.831	95.9	0.92 (0.354)	0.92 (0.449)	0.82 (0.418)	(0.618)
			NT	432	234	30	0.812					
	rs3766752	GG/GA/AA	HT	210	367	167	0.782	97.8	1.09 (0.225)	1.15 (0.235)	1.10 (0.433)	(0.454)
			NT	180	356	171	0.847					
	rs11808688	GG/GA/AA	HT	197	372	169	0.795	96.9	0.94 (0.389)	0.86 (0.183)	1.00 (0.985)	(0.370)
			NT	209	331	160	0.189					

Table S6 Continued

Gene	SNP (position)	Genotype		Screening Panel					Odds ratio (p-value)			
				Genotype frequency			HWE	Call rate	Allelic	Recessive	Dominant	Additive
ATP2B4	rs4951130	GG/GA/AA	HT	410	278	50	0.758	97.2	**1.21 (0.025)**	1.22 (0.058)	1.40 (0.086)	(0.082)
			NT	356	283	65	0.421					
	rs12095268	TT/TA/AA	HT	367	313	67	0.982	98.0	1.09 (0.303)	1.09 (0.439)	1.19 (0.335)	(0.556)
			NT	333	300	74	0.599					
	rs12410036	TT/TC/CC	HT	48	256	439	0.200	97.7	0.90 (0.232)	0.93 (0.720)	0.87 (0.196)	(0.434)
			NT	49	264	394	0.599					
	rs7547344	GG/GA/AA	HT	172	362	205	0.618	97.7	1.00 (0.977)	1.02 (0.875)	0.98 (0.846)	(0.954)
			NT	163	354	194	0.951					
	rs955865	GG/GA/AA	HT	208	368	173	0.677	98.6	0.95 (0.456)	0.96 (0.733)	0.89 (0.370)	(0.668)
			NT	204	359	151	0.765					
	rs955866	TT/TC/CC	HT	170	366	208	0.712	98.5	1.05 (0.489)	1.11 (0.401)	1.04 (0.756)	(0.702)
			NT	151	361	206	0.758					

The screening panel is comprised of 758 middle age-onset severe hypertensive patients and 726 middle-aged to elderly evidently normotensive controls (Table S4).

Table S7 Meta-analysis of ATP2B1 SNPs with hypertension

SNP	Coded Allele	Millennium GPJ			Global BPgen			Pooled		
		OR (95% CI)	P	N	OR (95% CI)	P	N	OR (95% CI)	P	N
rs1401982	A	1.19 (1.11-1.29)	$1.3*10^{-6}$	9,967	1.07 (1.02-1.12)	0.010	19126	1.10 (1.06-1.15)	$1.5*10^{-6}$	29,093
rs2681472	A	1.21 (1.13-1.30)	$1.8*10^{-7}$	10,039	1.14 (1.06-1.22)	$2.2*10^{-4}$	19055	1.17 (1.12-1.23)	$2.1*10^{-10}$	29,094
rs11105364	T	1.21 (1.13-1.30)	$1.5*10^{-7}$	10,014	1.13 (1.06-1.21)	$4.6*10^{-4}$	19151	1.17 (1.11-1.22)	$3.1*10^{-10}$	29,165
rs11105378	C	1.21 (1.13-1.30)	$1.5*10^{-7}$	9,972	1.13 (1.05-1.21)	$5.9*10^{-4}$	18894	1.17 (1.11-1.23)	$7.0*10^{-10}$	28,866

In both Japanese Millennium GPJ and Global BP gen, hypertensive subjects were defined as being treated with antihypertensive medication, or SBP greater or equal to 140 mmHg, or DBP greater or equal to 90 mmHg; normotensive subjects were defined as all of not treated with antihypertensive medication, and SBP less or equal to 120 mmHg, and DBP less or equal to 85 mmHg [8]. Adjusted odds ratio was calculated under additive model using multiple logistic regression analysis adjusted for age, age^2, sex, BMI, and cohort variables. Within Global BPgen, individual cohort results were combined using inverse variance weighted meta-analysis of the effects on a log-odds-ratio scale.

Table S8 Association of ATP2B1 SNPs and blood pressure traits in each Japanese cohort

SNP	coded allele		cohort				SBP			DBP		
	allele	%	name	n	HWE	CR	coefficient	SE	p	coefficient	SE	p
rs1401982	A	61.9	Ohasama	1569	0.227	98.6	0.35	0.60	0.558	0.06	0.39	0.868
		62.3	Yokohama	2269	0.588	99.1	-1.51	0.43	**$4.2*10^{-4}$**	-0.75	0.29	**0.009**
		62.6	Shigaraki	2191	0.908	96.4	-1.72	0.56	**0.002**	-0.91	0.35	**0.010**
		61.8	Takashima	1718	0.302	99.3	-1.95	0.72	**0.007**	-0.90	0.41	**0.028**
		61.7	Suita	2529	0.506	99.7	-0.80	0.57	0.160	-0.44	0.33	0.182
		62.0	Matsuyama	803	0.175	99.4	-1.27	0.97	0.194	-1.39	0.62	**0.026**
		63.8	Nomura	2865	0.611	99.6	-1.39	0.56	**0.020**	-0.67	0.33	**0.045**
rs2681472	A	62.1	Ohasama	1587	0.226	99.7	0.38	0.60	0.522	0.06	0.39	0.887
		62.6	Yokohama	2278	0.321	99.5	-1.52	0.43	**$3.8*10^{-4}$**	-0.78	0.28	**0.006**
		63.5	Shigaraki	2254	0.701	99.2	-2.03	0.56	**$2.9*10^{-4}$**	-1.15	0.35	**0.001**
		62.3	Takashima	1718	0.257	99.3	-2.25	0.72	**0.002**	-1.03	0.41	**0.013**
		62.1	Suita	2528	0.655	99.7	-0.97	0.57	0.089	-0.49	0.33	0.131
		62.1	Matsuyama	802	0.191	99.3	-1.13	0.98	0.248	-1.39	0.62	**0.026**
		64.3	Nomura	2865	0.907	99.6	-1.42	0.60	**0.018**	-0.69	0.34	**0.041**
rs11105364	T	62.2	Ohasama	1589	0.203	99.8	0.42	0.60	**0.477**	0.12	0.39	**0.766**
		63.3	Yokohama	2277	0.414	99.4	-1.61	0.43	**$1.8*10^{-4}$**	-0.79	0.29	**0.006**
		64.3	Shigaraki	2234	0.410	98.3	-2.11	0.56	**$1.7*10^{-4}$**	-1.16	0.35	**0.001**
		62.7	Takashima	1727	0.570	99.8	-2.25	0.71	**0.002**	-0.98	0.41	**0.017**
		62.4	Suita	2530	0.635	99.8	-1.08	0.57	**0.058**	-0.54	0.33	**0.096**
		62.8	Matsuyama	805	0.285	99.6	-1.05	0.98	**0.285**	-1.35	0.62	**0.031**
		64.4	Nomura	2851	0.495	99.1	-1.30	0.60	**0.030**	-0.60	0.34	**0.077**

Table S8 Continued

SNP	coded allele		cohort				SBP			DBP		
	allele	%	name	n	HWE	CR	coefficient	SE	p	coefficient	SE	p
rs11105378	C	62.9	Ohasama	1566	0.478	98.4	0.31	0.60	**0.600**	-0.04	0.39	**0.914**
		63.4	Yokohama	2258	0.244	98.6	-1.32	0.43	**0.002**	-0.66	0.29	**0.022**
		65.2	Shigaraki	2213	0.141	97.4	-2.45	0.56	**$1.3*10^{-5}$**	-1.31	0.35	**$2.2*10^{-4}$**
		63.2	Takashima	1722	0.237	99.5	-2.41	0.72	**$8.5*10^{-4}$**	-1.15	0.41	**0.006**
		63.0	Suita	2521	0.498	99.4	-1.00	0.58	**0.084**	-0.42	0.33	**0.207**
		63.2	Matsuyama	803	0.434	99.4	-1.14	0.99	**0.249**	-1.56	0.63	**0.014**
		65.7	Nomura	2865	0.468	99.6	-1.11	0.60	**0.065**	-0.47	0.34	**0.164**

Coefficients and standardized error for systolic and diastolic BP were calculated under additive model using multiple regression analysis adjusted for age, age2, sex, BMI. Adjustment for treatment with antihypertensive medication was achieved by adding fixed constants to measured values (+15mmHg for SBP and +10mmHg for DBP). CR indicates call rate.

Table S9 Association of European GWAS-derived SNPs with hypertension in the Japanese screening and replication panels

SNP	Genotype		Screening panel						Replication panel						overall
			Genotype frequency			HWE	Call rate	Odds (p value)	Genotype frequency			HWE	Call rate	Odds (p value)	Odds (p value)
FGF5 rs1458038	TT/TC/CC	HT	92	338	315	0.928	98.0	**1.19** **0.030**	271	838	788	0.047	97.9	**1.21** **$(1.1*10^{-4})$**	**1.20** **$(9.9*10^{-6})$**
		NT	81	281	347	0.039			225	801	918	0.014			
CYP17A1 rs1004467	AA/AG/GG	HT	380	299	66	0.514	98.6	**1.35** **$(1.4*10^{-4})$**	894	869	168	0.034	99.8	1.09 (0.079)	**1.16** **$(4.9*10^{-4})$**
		NT	309	308	101	0.089			877	901	205	0.236			
CSK rs1378942	CC/CA/AA	HT	483	236	25	0.557	98.0	1.09 0.340	1237	605	72	0.853	98.9	1.04 (0.536)	1.05 (0.305)
		NT	452	223	35	0.274			1259	621	85	0.449			
PLCD3 rs12946454	TT/TA/AA	HT	28	210	510	0.276	98.8	1.12 0.256	68	526	1339	0.070	99.7	0.99 (0.907)	1.03 (0.624)
		NT	13	207	499	0.107			68	545	1364	0.140			
PLEKHA7 rs381815	TT/TC/CC	HT	27	242	483	0.624	98.8	1.05 0.596	85	567	1273	0.033	99.4	0.99 (0.913)	1.01 (0.852)
		NT	31	208	475	0.181			93	574	1308	0.004			
CSK-ULK3 rs6495122	AA/AC/CC	HT	508	204	21	0.924	96.8	1.18 0.085	1289	561	72	0.263	99.2	1.10 (0.102)	**1.12** **(0.021)**
		NT	458	221	25	0.793			1267	626	77	0.976			
ULK4 rs9815354	AA/AG/GG	HT	7	142	598	0.654	98.5	0.90 0.374	31	385	1507	0.265	98.9	1.05 (0.463)	1.01 (0.873)
		NT	10	144	561	0.826			26	382	1548	0.659			

The screening panel is comprised of 758 middle age-onset severe hypertensive patients and 726 middle-aged to elderly evidently normotensive controls (Table S4). The replication panel consists of 1,929 hypertensive cases and 1,993 normotensives controls selected from a 11,569 cohort sample were enrolled (Table S2). Odds ratios and p-values for allelic model are shown.

Table S10 Association of European GWAS-derived SNPs and blood pressure traits in each Japanese cohort

SNP	coded allele		cohort				SBP			DBP		
	allele	%	name	n	HWE	CR	coefficient	SE	p	coefficient	SE	p
FGF5 rs1458038	T	33.7	Ohasama	1557	0.174	97.8	1.58	0.60	**0.008**	0.44	0.39	0.260
		33.5	Yokohama	2223	0.005	97.1	0.84	0.44	0.055	0.46	0.29	0.115
		33.8	Shigaraki	2156	0.001	94.9	1.17	0.56	0.037	0.46	0.35	0.196
		31.4	Takashima	1714	0.163	99.1	2.43	0.73	**0.001**	1.62	0.42	**$1.0*10^{-4}$**
		33.6	Suita	2533	0.508	99.9	0.67	0.58	0.250	0.43	0.33	0.191
		33.4	Matsuyama	804	0.459	99.5	0.70	1.04	0.500	0.54	0.67	0.414
		38.2	Nomura	2841	0.105	98.8	1.85	0.58	**0.002**	1.09	0.33	**0.001**
CYP17A1 rs1004467	A	70.2	Ohasama	1579	0.254	99.2	1.41	0.45	**0.002**	0.48	0.30	0.110
		68.4	Yokohama	2276	0.812	99.4	1.05	0.57	0.065	0.03	0.36	0.938
		65.5	Shigaraki	2244	0.898	98.7	1.46	0.74	**0.050**	0.83	0.43	0.051
		67.8	Takashima	1714	0.573	99.1	-0.21	0.59	0.721	-0.34	0.34	0.308
		66.8	Suita	2533	0.865	99.9	0.12	1.05	0.911	-0.10	0.67	0.885
		67.4	Matsuyama	804	0.388	99.5	1.25	0.62	0.045	0.50	0.35	0.149
		69.7	Nomura	2859	0.475	99.4	1.41	0.45	**0.002**	0.48	0.30	0.110
CSK rs1378942	C	77.7	Ohasama	1575	0.821	98.9	-0.17	0.68	0.804	-0.53	0.45	0.241
		78.1	Yokohama	2245	0.152	98.0	0.73	0.52	0.157	0.48	0.35	0.167
		83.0	Shigaraki	2225	0.187	97.9	1.80	0.71	0.012	1.35	0.45	**0.003**
		80.7	Takashima	1703	0.808	98.4	-0.41	0.88	0.644	0.08	0.51	0.870
		80.5	Suita	2528	0.098	99.7	1.28	0.69	0.063	0.43	0.39	0.270
		79.7	Matsuyama	798	0.846	98.8	0.24	1.21	0.842	0.07	0.77	0.923
		81.0	Nomura	2848	0.075	99.0	1.18	0.72	0.103	0.63	0.41	0.121

Table S10 Continued

SNP	coded allele		cohort				SBP			DBP		
	allele	%	name	n	HWE	CR	coefficient	SE	p	coefficient	SE	p
PLCD3 rs12946454	T	81.6	Ohasama	1583	0.356	99.4	1.76	0.72	**0.015**	0.99	0.48	**0.038**
		83.0	Yokohama	2274	0.517	99.3	0.23	0.56	0.687	0.12	0.37	0.752
		83.3	Shigaraki	2242	0.966	98.6	0.46	0.72	0.524	0.76	0.46	0.094
		85.3	Takashima	1712	0.707	99.0	-1.37	0.98	0.163	-1.09	0.56	0.052
		83.2	Suita	2528	0.234	99.7	0.53	0.73	0.464	0.08	0.42	0.845
		82.4	Matsuyama	805	0.799	99.6	0.34	1.28	0.790	0.86	0.82	0.290
		82.4	Nomura	2861	0.142	99.5	-0.35	0.75	0.635	-0.05	0.42	0.899
PLEKHA7 rs381815	T	15.1	Ohasama	1590	0.566	99.9	0.22	0.79	0.778	0.23	0.52	0.657
		19.7	Yokohama	2281	0.457	99.6	-0.77	0.52	0.139	0.04	0.35	0.900
		19.3	Shigaraki	2248	0.587	98.9	-0.38	0.68	0.574	-0.90	0.43	**0.034**
		19.0	Takashima	1719	0.434	99.4	-0.196	0.87	0.271	-0.22	0.50	0.660
		20.2	Suita	2527	0.421	99.6	0.76	0.69	0.272	0.42	0.40	0.289
		20.2	Matsuyama	808	0.496	100.0	0.99	1.19	0.408	0.53	0.76	0.489
		23.2	Nomura	2859	0.007	99.4	0.88	0.66	0.187	0.73	0.37	0.052
CSK-ULK3 rs6495122	A	79.4	Ohasama	1581	0.050	99.3	-0.39	0.69	0.569	-0.46	0.45	0.308
		78.4	Yokohama	2288	0.157	99.9	0.88	0.51	0.086	0.66	0.34	0.055
		83.5	Shigaraki	2237	0.146	98.4	0.96	0.72	0.183	0.96	0.45	**0.034**
		80.6	Takashima	1720	0.221	99.4	0.03	0.86	0.969	0.06	0.49	0.907
		81.6	Suita	2529	0.004	99.7	0.87	0.69	0.211	0.18	0.40	0.654
		81.5	Matsuyama	806	0.734	99.8	1.35	1.24	0.276	0.68	0.79	0.391
		82.6	Nomura	2855	0.115	99.3	1.16	0.75	0.120	0.64	0.42	0.129

Table S10 Continued

SNP	coded allele		cohort				SBP			DBP		
	allele	%	name	n	HWE	CR	coefficient	SE	p	coefficient	SE	p
ULK4 rs9815354	A	14.9	Ohasama	1569	0.749	98.6	-0.08	0.80	0.918	0.32	0.53	0.543
		10.5	Yokohama	2269	0.122	99.1	-1.01	0.67	0.134	-0.44	0.45	0.331
		12.7	Shigaraki	2252	0.099	99.1	-1.58	0.80	**0.047**	-0.10	0.50	0.846
		12.0	Takashima	1710	0.201	98.8	-0.57	1.08	0.600	0.15	0.62	0.802
		11.9	Suita	2521	0.456	99.4	-1.03	0.86	0.232	-0.08	0.49	0.867
		11.4	Matsuyama	804	0.389	99.5	-0.91	1.50	0.547	0.70	0.96	0.467
		9.1	Nomura	2853	0.632	99.2	0.79	1.00	0.427	1.21	0.56	**0.030**

Coefficients and standardized error for systolic and diastolic BP were calculated under additive model using multiple regression analysis adjusted for age, age2, sex, BMI. Adjustment for treatment with antihypertensive medication was achieved by adding fixed constants to measured values (+15mmHg for SBP and +10mmHg for DBP).

Table S11 Multiple linear regression analysis for BP trait and hypertension

Parameters	Coded allele	Systolic blood pressure			Diastolic blood pressure			Hypertension	
		Coefficient	Standardized coefficient	P	Coefficient	Standardized coefficient	P	Odds (95% C.I.)	p
Sex		2.38	0.05	<0.001	3.15	0.12	<0.001	1.33 (1.18-1.50)	<0.001
Age (years)		0.31	0.19	<0.001	0.96	1.03	<0.001	1.15 (1.12-1.19)	<0.001
Age^2		0.00	0.25	<0.001	-0.01	-0.74	<0.001	0.99 (0.99-0.99)	0.008
Body mass index (kg/m^2)		1.80	0.25	<0.001	1.12	0.27	<0.001	1.28 (1.26-1.30)	<0.001
Habitual drinking		0.79	0.02	0.035	0.93	0.04	<0.001	1.24 (1.11-1.40)	<0.001
ATP2B1 rs11105378	C	1.32	0.04	$4.4*10^{-8}$	0.71	0.04	$6.1*10^{-7}$	1.21 (1.12-1.30)	$4.0*10^{-7}$
FGF5 rs1458038	T	1.36	0.04	$1.5*10^{-8}$	0.77	0.04	$6.4*10^{-8}$	1.20 (1.11-1.29)	$1.4*10^{-6}$
CYP17A1 rs1004467	A	0.97	0.03	$8.9*10^{-5}$	0.35	0.02	0.017	1.14 (1.06-1.23)	$8.4*10^{-4}$
CSK rs1378942	C	0.71	0.02	0.014	0.36	0.02	0.036	1.09 (1.00-1.19)	0.046

Coefficients for systolic and diastolic BP were calculated using multiple linear regression analysis adjusted cohort variables. Adjustment for treatment with antihypertensive medication was achieved by adding fixed constants to measured values (+15mmHg for SBP and +10mmHg for DBP). Hypertensive subjects were defined as being treated with antihypertensive medication, or SBP greater or equal to 140 mmHg, or DBP greater or equal to 90 mmHg; normotensive subjects were defined as all of not treated with antihypertensive medication, and SBP less or equal to 120 mmHg, and DBP less or equal to 85 mmHg [8].

FIGURE S1

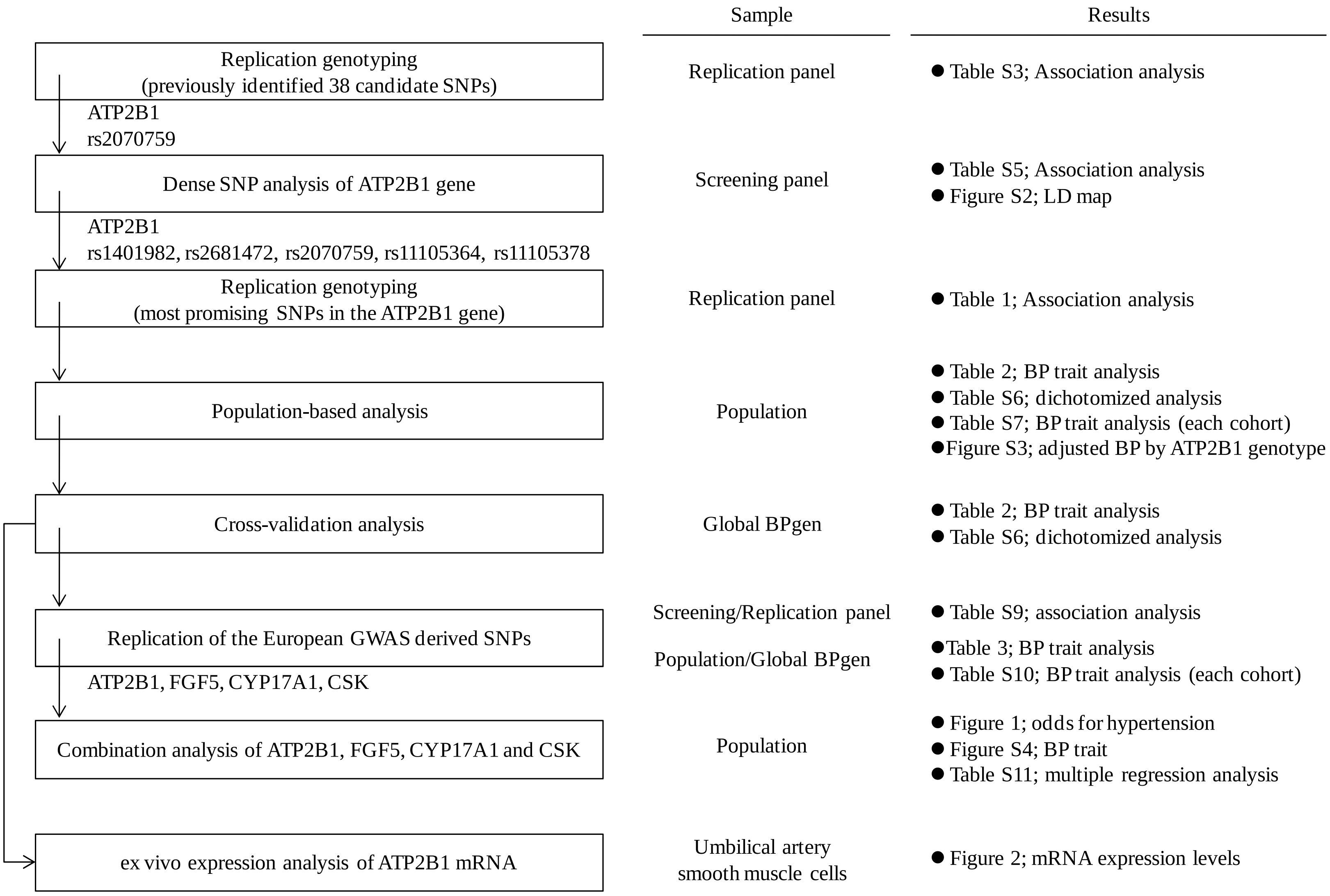

Figure S1 Study procedure and corresponding samples and results

FIGURE S2

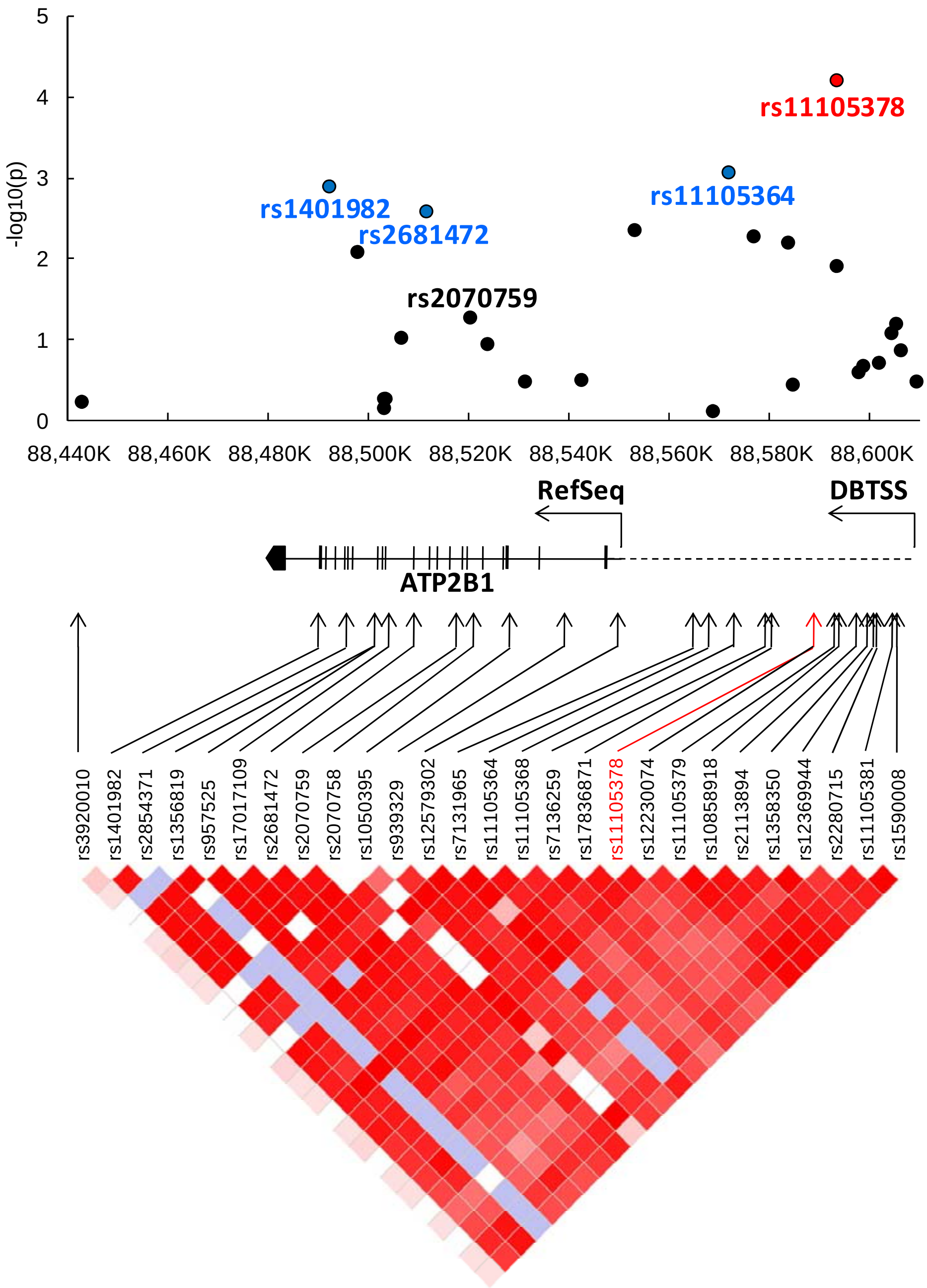

Figure S2 Dense SNP analysis of the ATP2B1 gene

The top graph shows p-values (-log10(P)) of association analyses using the screening panel (Table S4). The red circle (rs11105378) indicates the SNP showing the most significant association with hypertension. The lower panel shows a LD (D’) map based on the genotype frequency of the control subjects

FIGURE S3

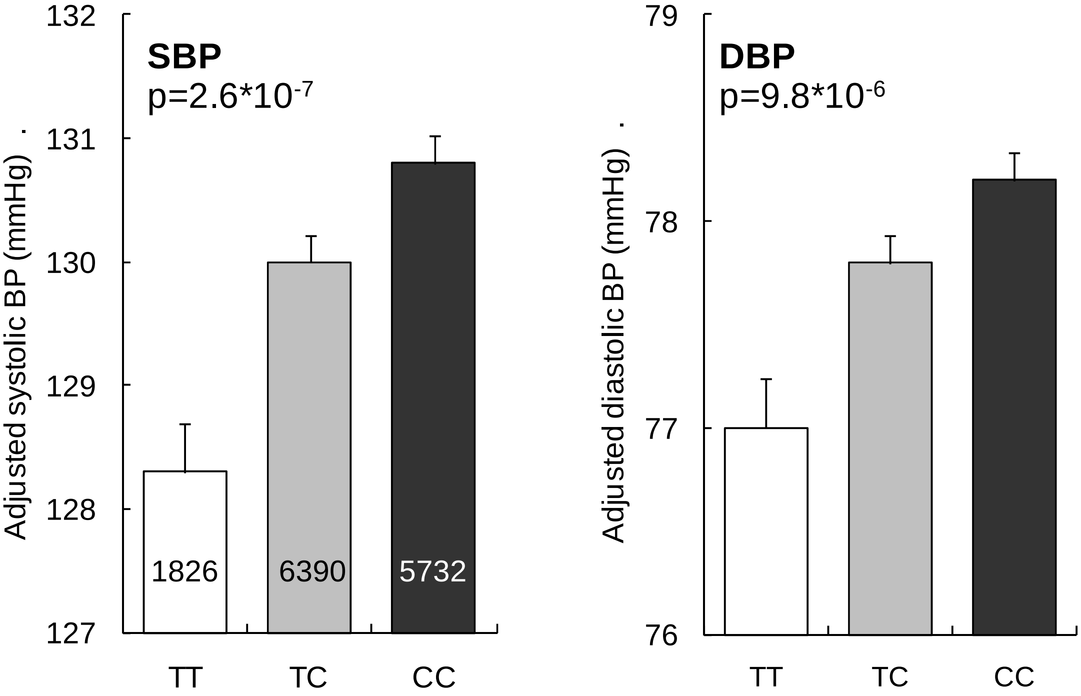

Figure S3 Adjusted systolic and diastolic BP among rs11105378 genotype

Values are mean±standard error adjusted for age, sex, body mass index, and cohort variables. Number of subjects in each genotype is represented in column.

FIGURE S4

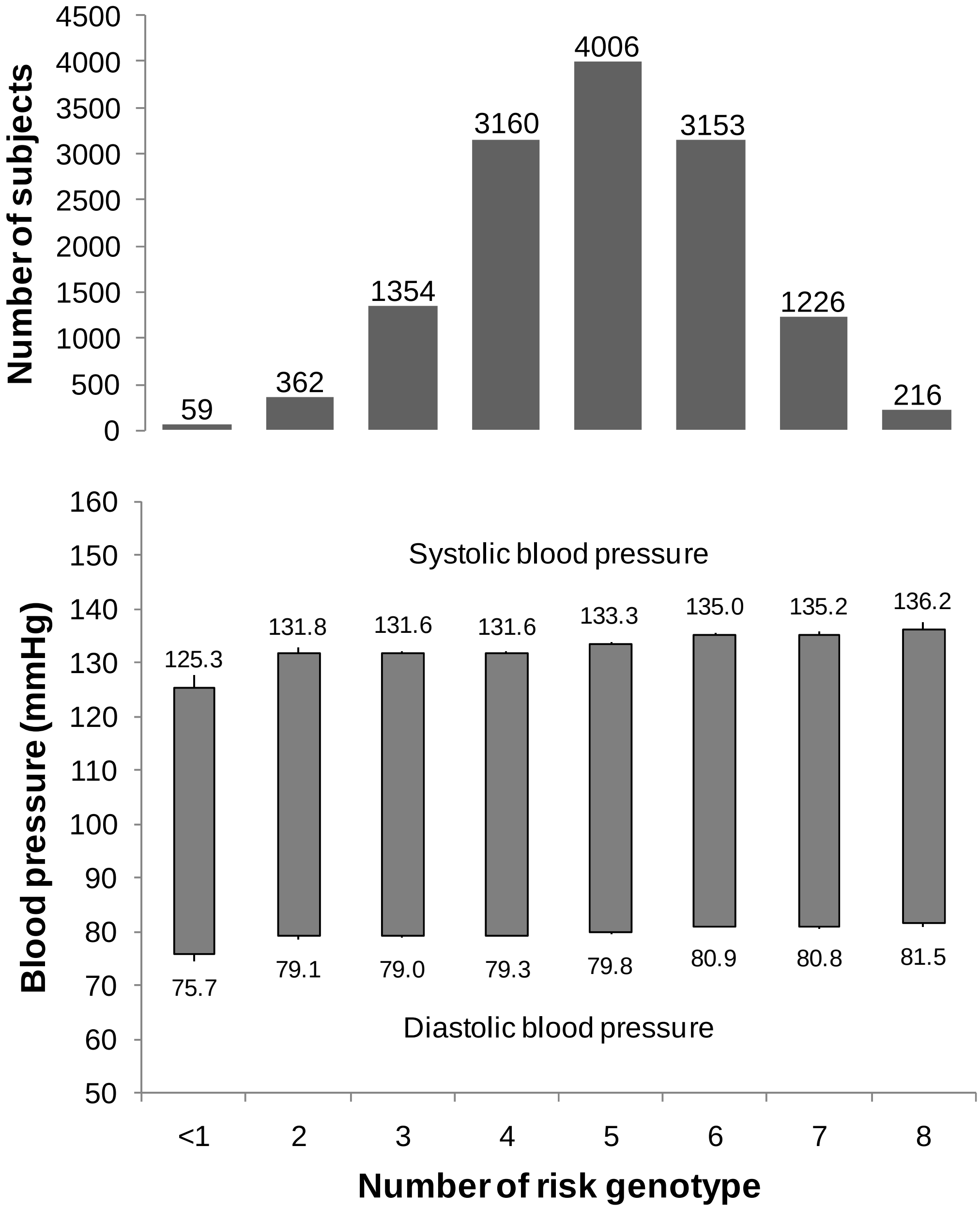

Figure S4 Adjusted blood pressure by the number of risk genotypes

Number of risk genotype was calculated by the following four SNPs; *ATP2B1* rs1105378, *FGF5* rs1458038, *CYP17A1*, rs1004467 and *CSK* rs1378942. Age, age2, sex, BMI and cohort variable adjusted systolic and diastolic BP is shown in the lower panel. Upper panel indicates the number of subjects in each group.

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