On-line/Supplementary Figure legends.

Supplementary Figure 1. Human *DBH* polymorphism discovery: Re-sequencing strategy. Sequences conserved between mouse and human DBH were visualized in VISTA. Location of common SNPs (solid rods) relative to exons and conserved non-coding sequences is indicated by position. Common haplotypes in each haplotype block are shown and connections between blocks are indicated by solid lines. Common haplotype blocks were constructed using HaploBlockFinder [(63)] with minimal haplotype coverage of 80% in each block. The chimp haplotype for the common SNPs is also shown.

Supplementary Figure 2. Human dopamine beta-hydroxylase (*DBH*): Functional domains and coding region (open reading frame) cSNPs.

Supplementary Figure 3. *DBH* promoter variant C-970T: Effects on plasma DBH activity in African Americans (A-A) and European American (E-A) subjects. Analyses were adjusted by age and sex. Error bars indicate mean ± SEM in each panel.
Left: Plasma DBH activity variation between European-American (E-A) and African-American (A-A) subjects.
Right. Plasma DBH activity in E-A and A-A subjects, as a function of promoter C-970T genotype.

Supplementary Figure 4. Replication: DBH promoter variant C-970T effects on BP in an independent population of Nigeria BP extreme groups. Variant -970T is associated with reduced systolic and diastolic BP in Nigerian subjects from population BP extremes (upper and lower quartiles of BP). Mean BP values ± SEM are shown, calculated from all individuals as indicated in each bar. Effects of genotypes on BP were evaluated using a general linear model (ANOVA), adjusted by age and sex (BP was untreated). Significant p values are shown.

Supplementary Figure 5. Replication: *DBH* promoter variant C-970T effects on BP in an independent population of San Diego unrelated individuals. Variant -970T is associated with reduced systolic BP in San Diego unrelated subjects. Analyses were adjusted by age, sex, self-identified ethnicity (because of the inclusion of more than one biogeographic ancestry group), and effect of antihypertensive medications (in treated hypertensives). Mean SBP values ± SEM are shown, calculated from all individuals as indicated in each bar.

Supplementary Figure 6: *DBH* promoter functional polymorphism C-970T: Baroreceptor function is intact in twin pairs. Downward and upward deflections measured in San Diego white twins are shown. Analyses were adjusted for age and sex. There were no trait differences among individuals stratified by C-970T genotype.

Supplementary Table 1. Descriptive statistics for the San Diego twin study.

	Normotensive (n=390)	Hypertensive (n=42)	p value
Age (years)	40.0±15.8	61.3±12.9	5.3E-14
Sex			
Male (n)	98	11	0.880
Female (n)	292	31	
Blood pressure (mmHg)			
Systolic	115.4±15.8	135.4±21.4	2.9E-12
Diastolic	62.7±11.8	73.3±14.9	4.5E-5
BMI (kg/m^2)	24.7±3.9	28.6±5.2	5.3E-7
Biogeographic ancestry	All white (European ancestry)	All white	-
BP treatment (%)	0%	90.5%	-

Descriptive statistics shown here are mean value ± one SD.

Supplementary Table 2. Descriptive statistics for the Nigeria (black) population BP extreme study (upper and lower 25^{th} %iles).

	Normotensive (n=190)	Hypertensive (n=193)	p value
Age (years)	53.5±11.0	50.1±13.8	0.008
Sex			
Male (n)	80	82	0.940
Female (n)	110	111	
Blood pressure (mmHg)			
Systolic	101.2±9.6	177.2±23.5	3.8E-115
Diastolic	66.1±8.2	102.9±17.9	2.0E-75
BMI (kg/m^2)	22.9±5.5	23.1±4.14	0.746
Biogeographic ancestry	All black (Nigerian)	All black	-
BP treatment (%)	0%	0%	-

Descriptive statistics shown here are mean value ± one SD.

Supplementary Table 3. Descriptive statistics for the San Diego BP unrelated individuals.

	Normotensive (n=611)	Hypertensive (n=367)	p
Age (years)	38.6±9.9	55.0±11.5	0.0008
Sex			
Male (n)	419	309	<0.0001
Female (n)	195	58	
Blood pressure (mmHg)			
Systolic	121.5±14.8	156.6±24.8	0.0001
Diastolic	70.4±9.9	89.8±15.3	0.0002
BMI (kg/m^2)	24.7±7.4	27.3±7.6	0.0002
Biogeographic ancestry			<0.0001
White	199	172	
Black	195	154	
Asian	57	12	
Hispanic	26	11	
Other/mixed	34	18	
BP treatment (%)	0%	64%	-

Descriptive statistics shown here are mean value ± one SD.

Supplementary Table 4. Summary of naturally occurring genetic variation at the human *DBH* locus in 4 populations.

Number	Variant major/minor	Position#	Amino acid change	RefSNP	Minor allele frequency (as a fraction) Asian(2N=32)	Black(2N=50)	Hispanic(2N=32)	White(2N=46)	Global(2N=160)
1	**gc/AT**	minus 2771-0	none	rs1076151/2	0.125	0.459	0.469	0.238	**0.494**
2&	**t/C**	minus 2734	none	rs1076150	0.031	0.416	0.188	0.432	**0.321**
3	t/C	minus 2253	none		0.068	0	0	0	0.017
4	c/*	minus 2251	none		0.068	0	0	0	0.017
5	g/A	minus 2239	none		0	0.02	0	0	0.006
6	**c/T**	minus 2073	none	rs1989787	0	0.06	0.125	0.438	**0.161**
7	g/A	minus 1986	none		0	0.1	0.031	0	0.034
8	ttt/***	minus 1524-2	none		0	0.06	0	0	0.018
9	g/A	minus 1446	none		0	0.08	0	0	0.024
10	c/T	minus 1381	none		0.023	0	0	0	0.006
11	**c/T**	minus 1282	none	rs1611114	0.773	0.46	0.429	0.237	**0.476**
12	a/G	minus 1109	none		0	0.06	0	0	0.018
13	a/G	minus 1059	none	rs3025377	0.068	0	0	0	0.006
14	g/T	minus 1027	none	rs12002610	0	0.02	0	0.023	0.018
15	**c/T**	minus 970	none	rs1611115	0.125	0.12	0.267	0.217	**0.178**
16	c/G	minus 757	none	rs1611116	0	0.02	0.067	0	0.017
17	c/T	minus 283	none		0.031	0	0	0	0.012
18	g/A	85, exon 1	V-12-M		0	0.02	0.313	0	0.011
19	g/A	409, intron 1	none		0	0.04	0	0	0.012
20&	**g/C**	457, intron 1	none	rs2797849	0	0.432	0.125	0.37	**0.259**
21	c/T	3437, intron 1	none	rs1611118	0	0	0.036	0.109	0.036
22&	**a/G**	3628, Exon 2	E-148-E	rs1108580	0.067	0.375	0.179	0.5	**0.404**
23	c/T	3641, intron 2	none	rs1611119	0	0	0.036	0.109	0.036
24	**g/A**	5815, intron 2	none	rs1611120	0.062	0.14	0.031	0.022	**0.074**
25	g/A	5889, exon 3	R-164-Q		0	0.02	0.031	0	0.011
26	a/G	5958, exon 3	N-187-S		0	0	0.031	0.022	0.011
27	**g/A**	5987, exon 3	A-197-T	rs5320	0.067	0.2	0.031	0.022	**0.091**
28	c/T	6091, exon 3	H-231-H	rs5322	0	0	0.031	0	0.006
29	c/T	6108, intron 3	none		0	0	0	0.022	0.006
30	c/T	6150, intron 3	none		0	0.02	0.031	0.109	0.04
31	g/A	7164, exon 4	D-270-N		0.031	0	0	0	0.006
32	g/A	7182, exon 4	D-276-N		0	0.04	0	0	0.011
33	**c/T**	7836, intron 4	none	rs1611125	0.067	0.48	0.219	0.435	**0.379**
34	c/T	7875, exon 5	Y-297-Y		0	0.02	0	0	0.006
35	g/T	7894, exon 5	A-304-S	rs4531	0	0.06	0.031	0.043	0.034
36&	**c/G**	7972, intron 5	none	rs1611126	0	0.3	0.063	0.09	**0.121**
37	**g/A**	8038, intron 5	none	rs1611128	0	0.04	0.125	0.391	**0.155**
38	t/C	9282, intron 5	none	rs3025405	0	0.02	0.125	0.043	0.04
39	g/A	11417, intron 5	none	rs3025411	0	0.06	0.036	0.071	0.042

40&	t/C	11694,	intron 6	none	rs1611129	0	0.12	0	0	0.034
41&	c/G	11714,	intron 6	none	rs1611130	0	0.16	0	0	0.046
42	g/A	11715,	intron 6	none		0.031	0	0	0	0.006
43&	**a/G**	15423,	intron 7	none	rs7862391	0	0.16	0.033	0	**0.052**
44	g/A	15472,	intron 7	none		0	0.08	0	0	0.023
45&	t/C	15520,	intron 7	none	rs10121827	0	0.14	0	0	0.04
46	(gtgtctg)2->3	15575,	intron 7	none		0	0.02	0	0	0.011
47	g/A	15584,	intron 7	none		0	0	0	0.022	0.006
48	a/C	15724,	intron 7	none		0	0	0	0.022	0.006
49	g/A	15815,	intron 7	none		0	0.04	0	0	0.011
50	g/A	16493,	intron 8	none	rs3025429	0	0.125	0	0	0.035
51	g/A	16519,	intron 8	none	rs129909	0	0.125	0	0	0.035
52	**g/A**	16608,	exon 9	T-456-T	rs77905	0.033	0.42	0.219	0.587	**0.341**
53	c/T	16757,	intron 9	none		0	0.021	0	0	0.006
54	c/T	16931,	intron 9	none		0	0.042	0	0	0.012
55	g/A	20115,	intron 9	none		0	0.02	0	0	0.006
56	g/A	20138,	intron 9	none		0.031	0	0	0	0.006
57	c/T	20418,	intron 10	none		0	0.02	0	0	0.006
58	c/T	20500,	intron 10	none		0.031	0	0	0	0.006
59	c/T	20570,	intron 10	none		0	0.08	0.032	0	0.029
60	**a/G**	20698,	intron 10	none	rs1611131	0.4	0.14	0.406	0.261	**0.276**
61	c/T	20785,	exon 11	R-535-C		0	0	0.032	0.022	0.011
62	c/T	20866,	intron 11	none		0	0.02	0	0	0.006
63	g/T	20875,	intron 11	none		0.033	0	0	0	0.006
64	g/A	22131,	exon12 UTR	none		0	0.02	0	0	0.006
65	c/T	22156,	exon12 UTR	none		0	0.02	0	0	0.006
66	a/G	22162,	exon12 UTR	none		0.031	0	0	0	0.006
67	**c/T**	22173,	exon12 UTR	none	rs129882	0.218	0.24	0.343	0.205	**0.25**
68	t/C	22351,	exon12 UTR	none	rs129914	0.063	0.065	0	0	0.041
69	**g/A**	22463,	exon12 UTR	none	rs13306304	0.25	0.042	0	0.045	**0.087**
70	c/T	22488,	exon12 UTR	none		0	0	0.032	0.023	0.012

&: Indicates the minor allele is the ancestral allele as determined by chimp and bonabo alleles. #: Positions are numbered with respect to transcription initiation (exon-1 start) site (which is +1). *: Indicates nucleotide deletion. ∆: Previously reported as –1021 with calculation from the translational start site (ATG) as +1 (14). Highlighted (**bold**) SNPs are common variants (minor allele frequency >5%) that subsequently were genotyped for DBH activity association studies. Major allele in lower case (atgc), minor allele in upper case (ATGC). 2n = number of chromosomes (= 2 * number of individuals).

Supplementary Table 5. Promoter region haplotypes (based on different numbers of SNPs) in population analyses and *in cella* studies.

***5A**: DBH* extended promoter 7-SNP haplotype distribution among San Diego white twins.

Promoter haplotype numbers	Nucleotide at position (upstream of cap site) -2771	-2770	-2734	-2073	-1282	-970	+457	Frequency, % in indicated population San Diego twins
7H-1	G	C	T	C	C	T	G	21.0%
7H-2	G	C	C	T	C	C	C	20.1%
7H-3	G	C	T	C	C	C	G	16.2%
7H-4	G	C	C	C	C	C	G	13.9%

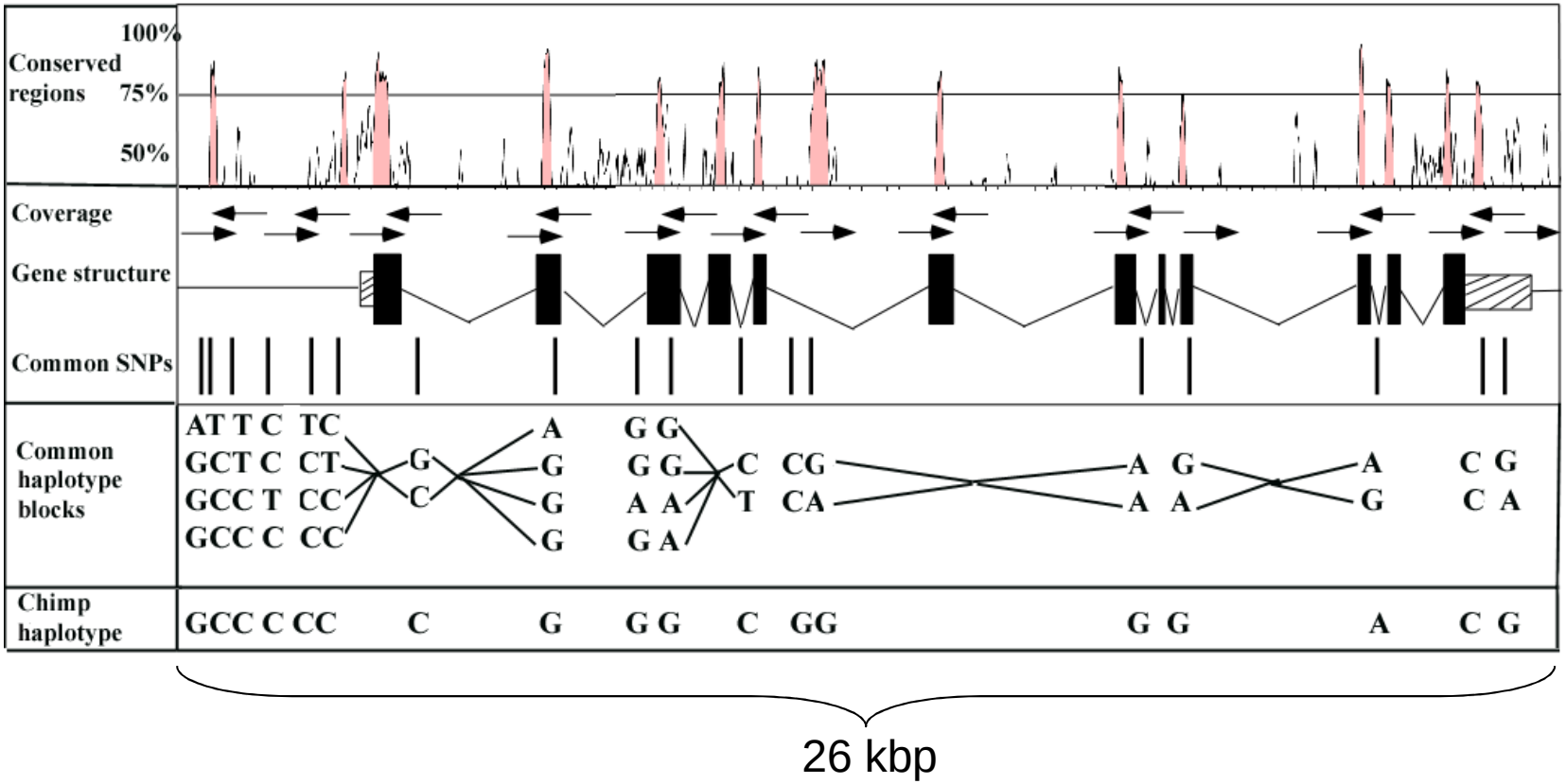
***5B**: DBH* promoter 4-SNP haplotype distribution in the black (Nigeria) BP extreme sample.

Promoter haplotype number	Nucleotide at position (upstream of cap site) -2734	-2073	-1282	-970	Frequency, % in indicated population Black (Nigeria) extremes
4H-1	T	C	T	C	28.0%
4H-2	T	C	C	T	14.3%
4H-3	C	T	C	C	6.6%
4H-4	C	C	C	C	43.6%

***5C**: DBH* promoter natural and mutant haplotypes inserted into the pGL3-Basic luciferase reporter vector.

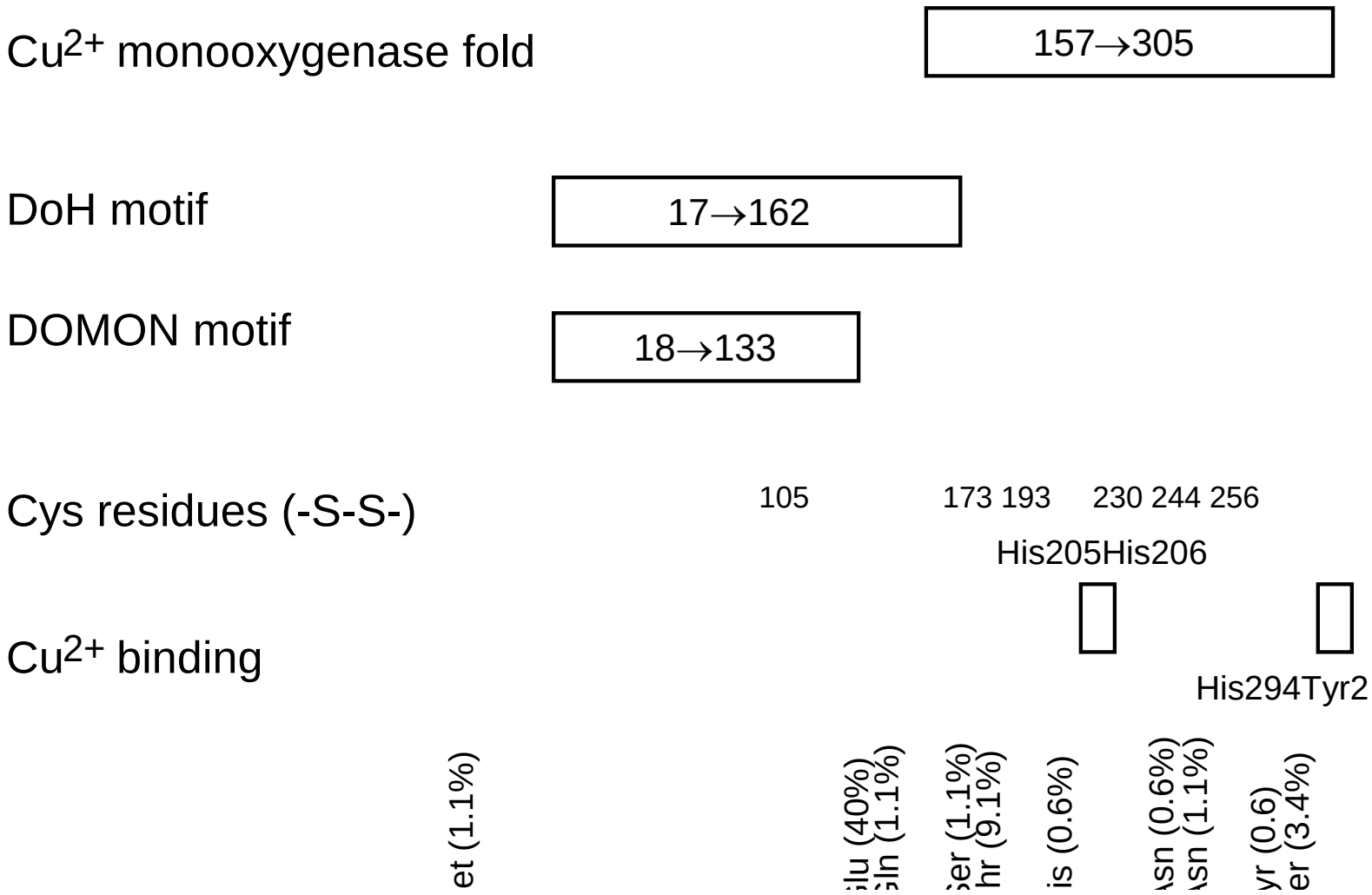
Haplotype number	Nucleotide at position (upstream of cap site) -2771	-2770	-2734	-2073	-1282	-970	Note
6H-1	A	T	T	C	T	C	Natural 6-SNP haplotype-1
6H-2	G	C	T	C	C	T	Natural 6-SNP haplotype-2
6H-3	G	C	C	T	C	C	Natural 6-SNP haplotype-3
6H-4	G	C	C	C	C	C	Natural 6-SNP haplotype-4
6H-1’	A	T	T	C	T	T	Mutation to -970T from 6H-1
6H-2’	G	C	T	C	C	C	Mutation to -970C from 6H-2
6H-3’	G	C	C	T	C	T	Mutation to -970T from 6H-3
6H-4’	G	C	C	C	C	T	Mutation to -970T from 6H-4

Human *DBH* polymorphism discovery: Resequencing strategy



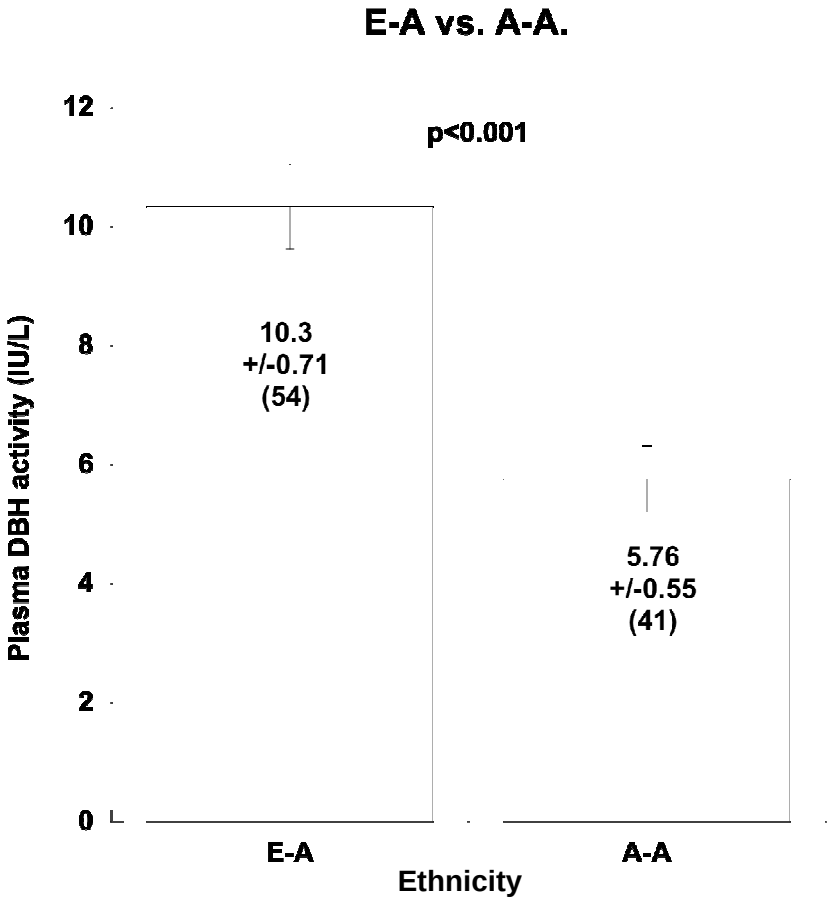
Suppl. Figure 1

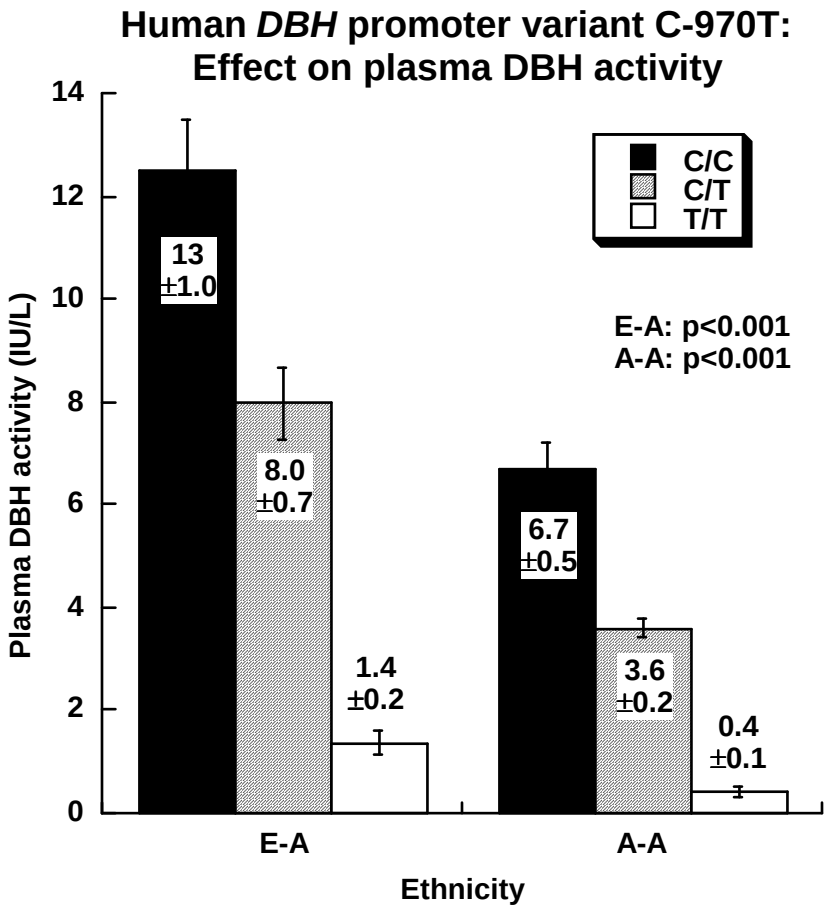
Human dopamine β-hyd
Functional domains and c



Suppl. Figure 2

DBH common variants: Effects on plasma DBH activity in Americans of African (A-A) or European (E-A) ancestry.

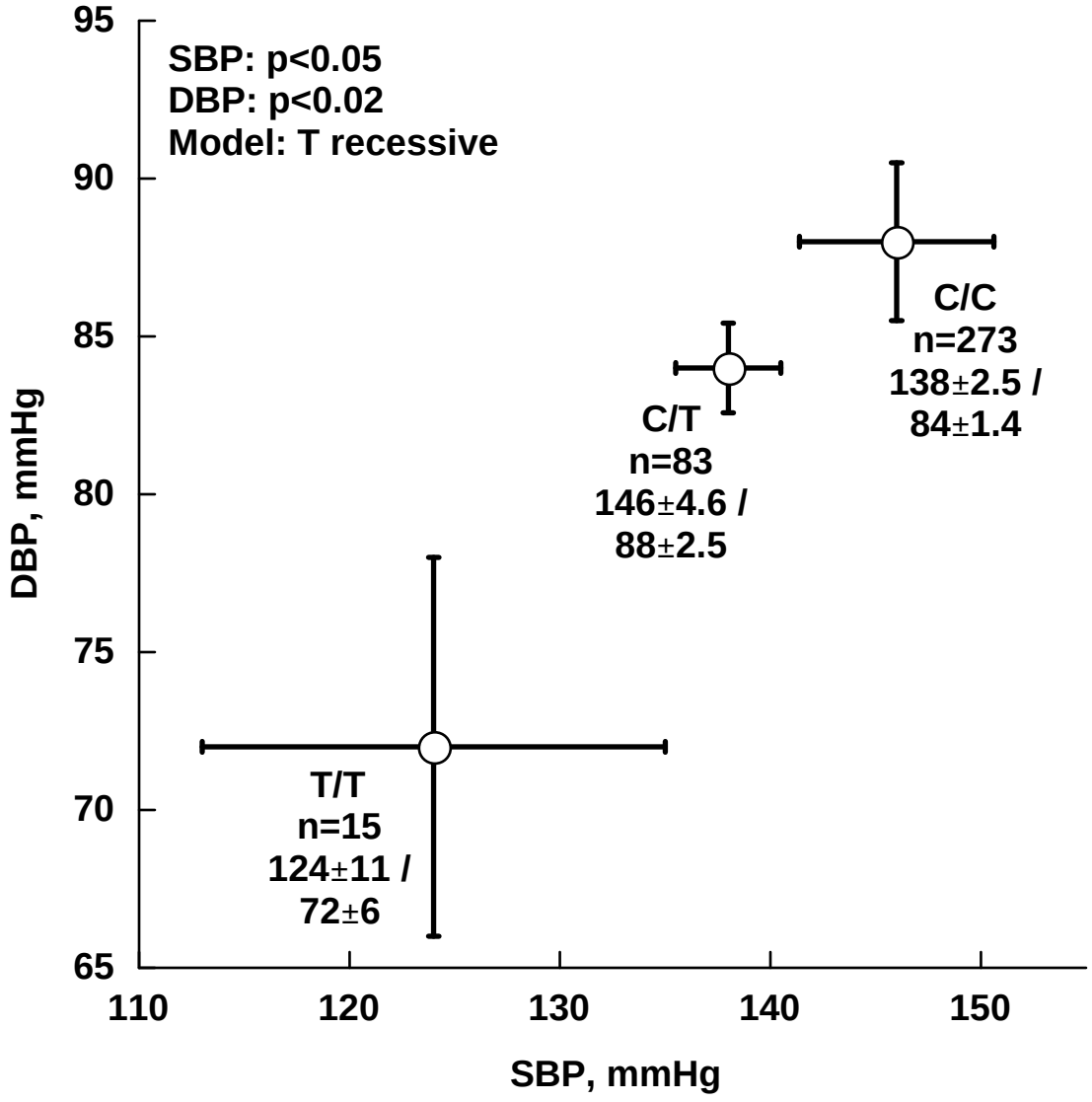




Suppl. Figure 3

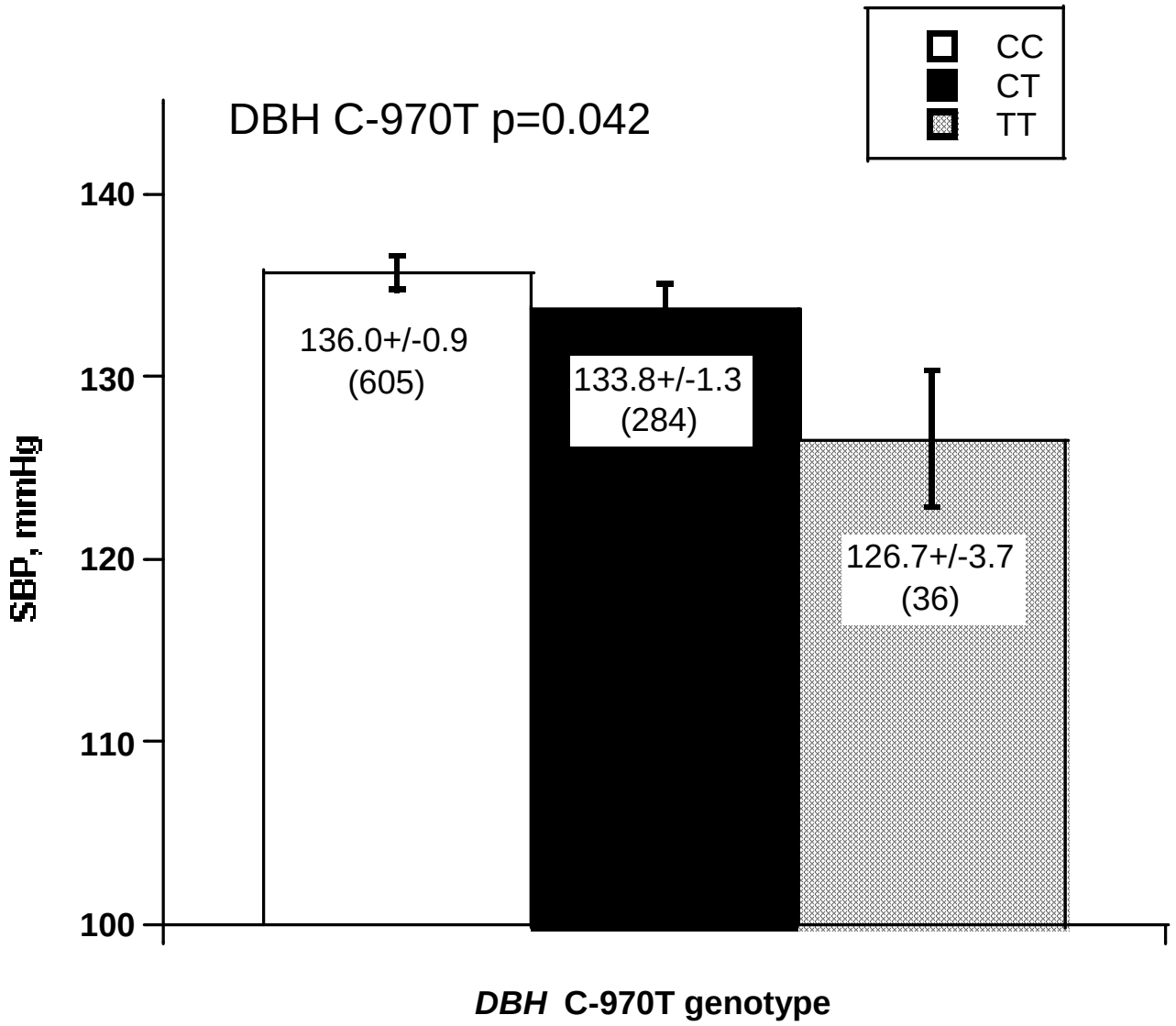
Replication: *DBH* variant C-970T effects on BP in an independent population.

African (Nigeria) population BP extremes.

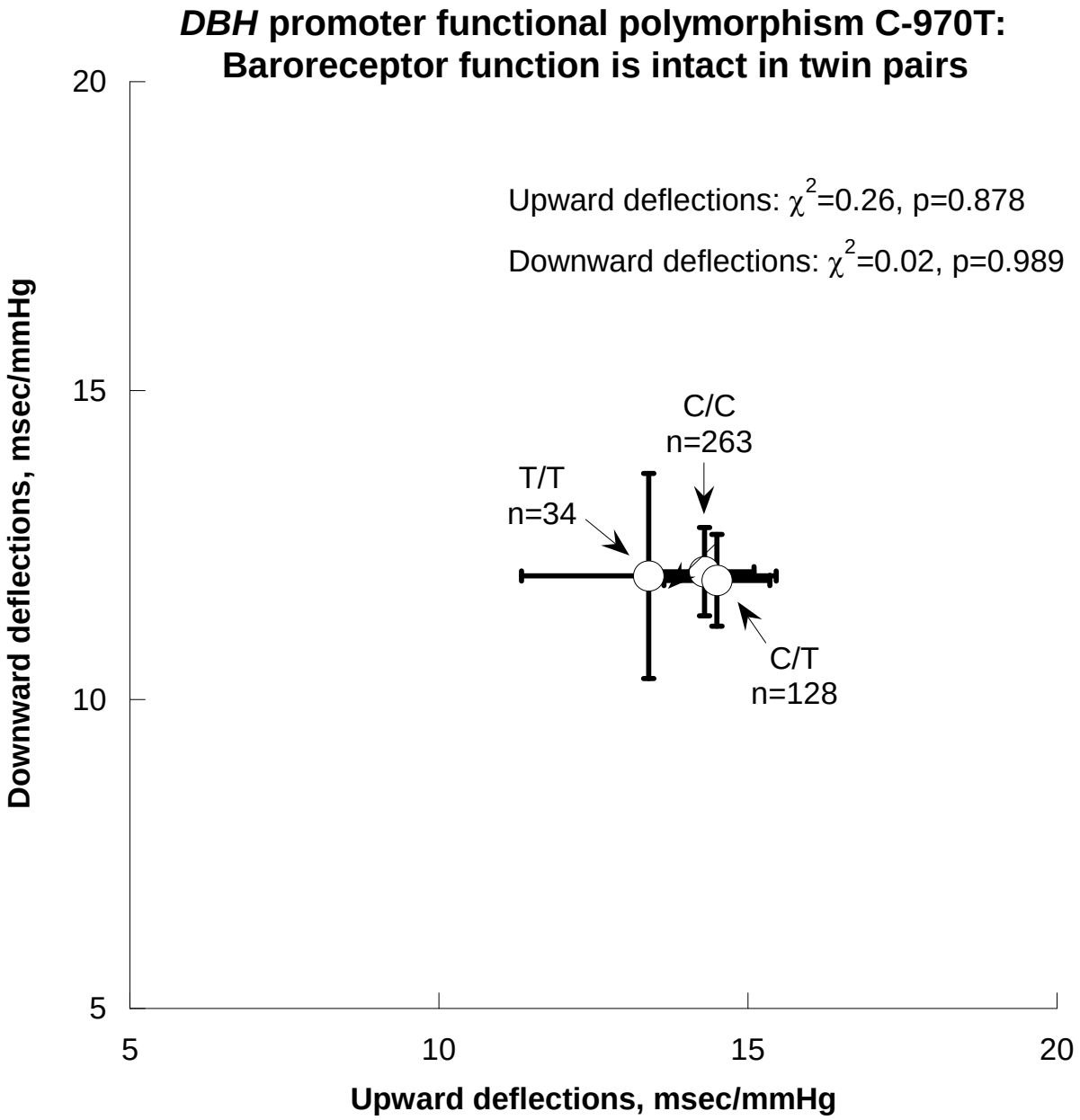


Suppl. Figure 4

Replication: *DBH* promoter variant C-970T effects on BP in independent population of San Diego unrelated individuals



Suppl. Fig. 5



Suppl. Figure 6