

**G PROTEIN RECEPTOR KINASE 4 (GRK4) POLYMORPHISMS: BETA-BLOCKER
PHARMACOGENETICS AND TREATMENT RELATED OUTCOMES IN HYPERTENSION**

Supplemental Material

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Table S1. Variant allele frequencies

	GRK4 R65L	GRK4 A142V	GRK4 A486V	ADRB1
	(T allele)	(T allele)	(T allele)	R389G
				(G allele)
PEAR				
African Americans (YRI, ASW)	0.49 (0.54, 0.57)	0.62 (0.65, 0.56)	0.14 (0.10, 0.10)	0.41 (0.41,n/a)
Caucasians (CEU)	0.34 (0.38)	0.36 (0.40)	0.42 (0.39)	0.26 (0.32)
INVEST				
African Americans (YRI, ASW)	0.40 (0.54, 0.57)	0.55 (0.65, 0.56)	0.12 (0.10, 0.10)	0.38 (0.41,n/a)
Caucasians (CEU)	0.34 (0.38)	0.36 (0.40)	0.39 (0.39)	0.27 (0.32)
Hispanics (MEX*)	0.33 (0.39)	0.38 (0.39)	0.34 (0.42)	0.30 (n/a)

The variant allele corresponding to GRK4 65L, 142V, 486V, and ADRB1 389G is indicated.

Variant allele frequencies are listed in the table. Number in parenthesis are from HapMap 3 Data: Yoruba in Idaban, Nigeria (YRI), African Ancestry in the Southwest UAS (ASW), Utah residents with ancestry from northern and western Europe (CEU), and Mexican ancestry in Los Angeles CA (MEX). *Note – the Hispanics in INVEST were mostly from Puerto Rico, whose inhabitants have different ancestry/admixture than those from Mexico. n/a, not available.

Table S2. BP response by GRK4 genotype in PEAR.

		Combined			
Drug Therapy		R65R	R65L	L65L	P _{trend}
Atenolol	n	142	171	62	
	SBP	-9.9 ± 10.3	-6.8 ± 10.4	-5.9 ± 11.3	0.0880
	DBP	-9.5 ± 6.7	-6.7 ± 7.2	-6.1 ± 6.4	0.0233*
HCTZ	n	130	165	70	
	SBP	-8.6 ± 8.9	-10.3 ± 9.2	-7.6 ± 7.6	0.2761
	DBP	-4.8 ± 6.3	-5.9 ± 5.8	-4.4 ± 5.5	0.4234
		A142A	A142V	V142V	
Atenolol	n	128	163	87	
	SBP	-10.4 ± 9.8	-7.8 ± 10.7	-4.1 ± 10.3	0.0461*
	DBP	-9.8 ± 6.6	-7.3 ± 7.3	-5.1 ± 6.2	0.0170*
HCTZ	n	105	172	95	
	SBP	-8.5 ± 9.5	-9.7 ± 8.8	-9.7 ± 8.9	0.8195
	DBP	-4.5 ± 5.9	-5.7 ± 5.8	-5.9 ± 6.2	0.5757
		A486A	A486V	V486V	
Atenolol	n	193	136	51	
	SBP	-7.0 ± 10.7	-8.1 ± 10.2	-10.3 ± 10.9	0.3097
	DBP	-7.3 ± 7.1	-7.8 ± 6.9	-8.5 ± 6.9	0.0133*
HCTZ	n	181	149	42	

	SBP	-10.2 ± 9.2.	-8.8 ± 9.2	-8.0 ± 7.4	0.4429
	DBP	-6.1 ± 6.3	-5.1 ± 5.9	-3.6 ± 3.9	0.1890
Caucasians					
		R65R	R65L	L65L	P_{trend}
Atenolol	n	109	88	32	
	SBP	-11.6 ± 9.7	-10.1 ± 9.2	-11.0 ± 9.2	0.2546
	DBP	-10.7 ± 6.2	-9.2 ± 6.5	-9.0 ± 6.3	0.0690
HCTZ	n	97	96	33	
	SBP	-7.0 ± 8.2	-8.6 ± 7.6	-7.0 ± 9.5	0.8588
	DBP	-3.9 ± 5.9	-4.9 ± 4.6	-3.3 ± 5.0	0.7955
		A142A	A142V	V142V	
Atenolol	n	104	99	28	
	SBP	-11.5 ± 9.8	-10.2 ± 9.3	-10.8 ± 8.9	0.4039
	DBP	-10.8 ± 6.2	-9.2 ± 6.6	-8.6 ± 5.8	0.0572
HCTZ	n	87	99	39	
	SBP	-7.8 ± 8.8	-8.2 ± 7.5	-6.2 ± 8.5	0.5455
	DBP	-4.0 ± 5.6	-4.7 ± 5.3	-3.5 ± 5.0	0.9674
		A486A	A486V	V486V	
Atenolol	n	83	101	49	
	SBP	-12.2 ± 8.9	-10.1 ± 9.1	-10.3 ± 10.6	0.1560
	DBP	-11.1 ± 6.0	-9.4 ± 6.3	-8.6 ± 6.9	0.0143*
HCTZ	n	76	111	38	

	SBP	-7.7 ± 8.1	-7.7 ± 8.6	-7.7 ± 7.4	0.7177
	DBP	-3.9 ± 5.1	-4.7 ± 5.9	-3.4 ± 3.7	0.8449
African Americans					
		R65R	R65L	L65L	P_{trend}
Atenolol	n	33	83	30	
	SBP	-5.3 ± 10.5	-3.3 ± 10.5	-0.6 ± 11.0	0.1073
	DBP	-6.0 ± 6.8	-3.9 ± 7.0	-3.0 ± 5.1	0.1218
HCTZ	n	33	69	37	
	SBP	-11.8 ± 9.0	-12.8 ± 10.5	-9.2 ± 7.9	0.1446
	DBP	-7.3 ± 6.4	-7.2 ± 6.9	-5.9 ± 6.2	0.3388
		A142A	A142V	V142V	
Atenolol	n	24	64	59	
	SBP	-5.6 ± 8.9	-4.6 ± 11.9	-0.9 ± 9.5	0.0356*
	DBP	-5.9 ± 6.9	-4.4 ± 7.3	-3.4 ± 5.7	0.1420
HCTZ	n	18	73	56	
	SBP	-11.3 ± 12.9	-11.6 ± 9.8	-12.0 ± 8.7	0.8873
	DBP	-6.1 ± 7.8	-6.7 ± 6.3	-7.5 ± 6.7	0.5358
		A486A	A486V	V486V	
Atenolol	n	110	35	2	
	SBP	-3.5 ± 10.3	-2.3 ± 11.3	-11.0 ± 23.9	0.7028
	DBP	-4.7 ± 6.5	-2.8 ± 6.8	-5.5 ± 10.6	0.3082
HCTZ	n	105	38	4	

SBP	-11.9 ± 9.7	-11.7 ± 10.3	-7.9 ± 6.5	0.2789
DBP	-7.4 ± 6.8	-5.9 ± 6.1	-3.8 ± 5.9	0.0282*

Table S3. BP response by GRK4 R65L-A142V haplotype in PEAR.

		Combined			
Drug Therapy		0 Copies of 65R-142A	1 copy of 65R-142A	2 Copies of 65R-142A	P _{trend}
Atenolol	n	105	163	112	
	SBP	-4.8 ± 10.4	-7.8 ± 10.5	-10.9 ± 9.9	0.0911
	DBP	-5.5 ± 6.2	-7.2 ± 7.3	-10.4 ± 6.4	0.0187*
HCTZ	n	187	127	108	
	SBP	-9.4 ± 8.8	-10.0 ± 9.9	-8.2 ± 9.4	0.5238
	DBP	-5.4 ± 6.2	-5.9 ± 5.8	-4.4 ± 5.9	0.6873
		0 Copies of 65L-142V	1 copy of 65L-142V	2 Copies of 65L-142V	P _{trend}
Atenolol	n	161	175	44	
	SBP	-9.5 ± 10.1	-7.0 ± 10.5	-4.7 ± 11.5	0.0204*
	DBP	-9.1 ± 6.8	-6.8 ± 7.1	-5.3 ± 6.4	0.0088*
HCTZ	n	142	181	50	
	SBP	-8.8 ± 9.1	-10.3 ± 9.1	-7.7 ± 7.9	0.4586
	DBP	-4.9 ± 6.3	-5.8 ± 5.8	-5.1 ± 5.5	0.9144
		Caucasians			
		0 Copies of 65R-142A	1 copy of 65R-142A	2 Copies of 65R-142A	P _{trend}

Atenolol	n	37	97	99	
	SBP	-11.3 ± 8.9	-9.9 ± 9.1	-11.6 ± 9.9	0.4157
	DBP	-9.1 ± 6.1	-9.2 ± 6.4	-10.8 ± 6.3	0.0622
HCTZ	n	46	100	80	
	SBP	-6.8 ± 9.6	-8.5 ± 7.4	-7.2 ± 8.2	0.5494
	DBP	-3.3 ± 5.4	-5.1 ± 5.1	-3.7 ± 5.4	0.6632
		0 Copies of	1 copy of	2 Copies of	P_{trend}
		65L-142V	65L-142V	65L-142V	
Atenolol	n	117	93	23	
	SBP	-11.6 ± 9.5	-10.1 ± 9.4	-10.3 ± 9.3	0.2121
	DBP	-10.7 ± 6.1	-9.2 ± 6.7	-8.3 ± 5.9	0.0589
HCTZ	n	105	95	26	
	SBP	-7.6 ± 8.7	-8.2 ± 7.7	-6.2 ± 7.7	0.8607
	DBP	-4.1 ± 6.0	-4.7 ± 4.8	-3.5 ± 4.2	0.8482
African Americans					
		0 Copies of	1 copy of	2 Copies of	P_{trend}
		65R-142A	65R-142A	65R-142A	
Atenolol	n	68	66	13	
	SBP	-1.4 ± 9.7	-4.6 ± 11.6	-6.4 ± 9.5	0.0764
	DBP	-3.7 ± 5.5	-4.2 ± 7.6	-7.7 ± 6.0	0.1382
HCTZ	n	69	64	14	

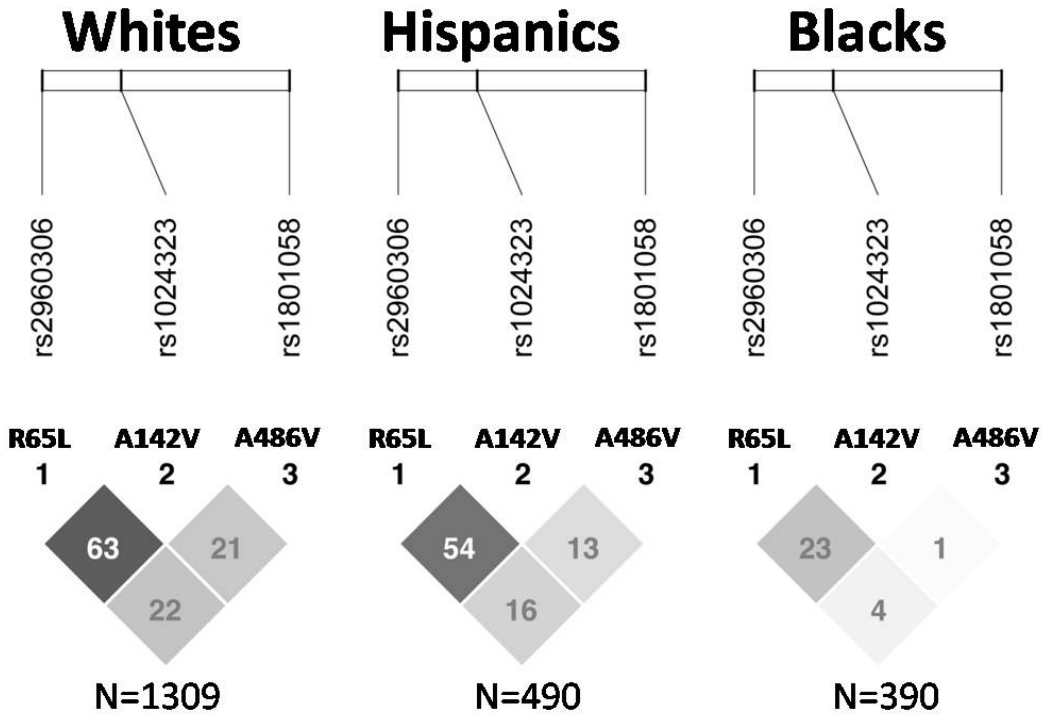
		0 Copies of 65L-142V	1 copy of 65L-142V	2 Copies of 65L-142V	P_{trend}
	SBP	-11.3 ± 80.5	-12.3 ± 10.5	-11.2 ± 12.4	0.7291
	DBP	-6.8 ± 6.5	-7.1 ± 6.6	-6.5 ± 7.4	0.9841
Atenolol	n	44	82	21	
	SBP	-5.2 ± 10.0	-3.5 ± 10.7	1.4 ± 10.8	0.0270*
	DBP	-5.5 ± 6.9	-4.2 ± 6.7	-2.1 ± 5.3	0.0843
HCTZ	n	37	86	24	
	SBP	-11.8 ± 9.8	-12.3 ± 10.1	-9.7 ± 8.3	0.2729
	DBP	-7.0 ± 6.8	-6.8 ± 6.6	-6.9 ± 6.4	0.6524

Table S4. Risk per variant allele of experiencing the primary outcome by treatment group

Nonblacks (Caucasians and Hispanics)			
Genotype	Odds Ratio	95% Confidence Interval	P value
R65L (All)	1.22	0.98-1.52	0.0779
R65L (CCB)	1.25	0.92-1.70	0.1507
R65L (BB)	1.22	0.88-1.70	0.2383
A142V (All)	1.25	1.01-1.54	0.0460*
A142V (CCB)	1.23	0.91-1.65	0.1780
A142V (BB)	1.28	0.97-1.77	0.1337
A486V (All)	1.47	1.18-1.83	0.0005*
A486V (CCB)	1.58	1.18-2.12	0.0024*
A486V (BB)	1.32	0.95-1.84	0.0973

Calcium channel blocker treatment strategy (CCB); β -Blocker strategy (BB)

Figure S1. GRK4 linkage disequilibrium plots.



R^2 based on pooled samples from PEAR and INVEST is shown for GRK4 SNPs in each of the three race groups examined.