

## ONLINE SUPPLEMENT

### Relationships Between Selected Gene Polymorphisms and Blood Pressure Sensitivity to Weight Loss in Elderly Persons with Hypertension

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Kostis: Polymorphisms associated with weight sensitivity of BP

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Table S1. Clinical variable selection

Variables in the model	Label	glmnet Coefficient	Change in SBP predicted by BMI	Change in DBP predicted by BMI	Change in SBP or DBP predicted by BMI
RV_DIABETES*	Diabetes requiring insulin	0.144172239	X	X	X
RV_LIGHT*	Number of hours light activity per day	-0.032537579	X	X	X
RV_BLOCKS*	Number of blocks per day	-0.024896784	X		X
RV_EXYEAR*	Rate of activity in the past year	0.165451851	X		X
RV_MOD*	Number of hours moderate activity per day	0.057056787	X		X
RV_DIAB_KIDX*	Diabetes - Child	-5.829650858	X		X
RV_KDNY_POPX*	Kidney failure - Father	1.020510836	X		X
RV_SMOKECUR*	Current smoker	0.987904456		X	X
RV_STRK*	Have they ever had a stroke	.		X	X
AGE	Age	.			
MALE1	Gender	.			
RV_RACE	Race	.			
RVWGT	Weight at randomization	.			
WT_CHNG	Change in weight from randomization to F/U	0.31206373			
RV_UNA	24 hour urine sodium at randomization	.			
CHUNA	Change in urine sodium	.			
F9_TOTCAL*	Food total calcium at F/U visit 9	.			
RV_HBP_AGE*	Age learned they had high blood pressure	.			
RV_MED_AGE*	Age began taking BP meds	0.001321736			
RV_HRTCOND*	Have they ever had a heart attack	.			
RV_EXWEEK*	Times exercise per week	.			
RV_FLIGHTS*	Number of flights per day	.			
RV_VIG*	Number of hours vigorous activity per day	.			
RV_SNOOZE*	Number of hours of sleep per day	.			
RV_HBP_POPX*	High blood pressure - Father	.			
RV_HBP_MOMX*	High blood pressure - Mother	.			
RV_HBP_BROX*	High blood pressure - Brother	.			
RV_HBP_SISX*	High blood pressure - Sister	.			
RV_HBP_KIDX*	High blood pressure - Child	.			
RV_DIAB_POPX*	Diabetes - Father	.			
RV_DIAB_MOMX*	Diabetes - Mother	.			
RV_DIAB_BROX*	Diabetes - Brother	.			
RV_DIAB_SISX*	Diabetes - Sister	.			
RV_KDNY_MOMX*	Kidney failure - Mother	.			
RV_KDNY_BROX	Kidney failure - Brother	.			

\* Denotes those variables that were in the set of investigator-selected covariates (described on page 7)

Table S2. Changes in SBP, DBP, BMI, and 24-hour urine sodium between baseline and the first drug withdrawal visit in the seven data subsets

Subset	Patients		Observations						
	N	Variable	N	Mean	STD	SE	Median	Minimum	Maximum
Attention control (subsets d & f)	243	SBP_Change	233	-0.69	12.49	0.82	0	-54	33
		DBP_Change	233	-0.58	7.68	0.50	0.00	-24.00	21.00
		BMI_Change	217	-0.05	0.68	0.05	0.00	-2.23	1.7
		24-hour_urine_sodium_Change	214	-9.35	62.11	4.25	-4.6	-253.94	128.7
Weight loss (subset b)	112	SBP_Change	110	-3.3	13.44	1.28	-4.5	-30	46
		DBP_Change	110	-0.74	10.40	0.99	-2.50	-17.00	58.00
		BMI_Change	106	-1.55	1.03	0.10	-1.44	-5.01	0.78
		24-hour_urine_sodium_Change	102	-6.72	62.83	6.22	-4.32	-186.95	132.58
Sodium reduction (subsets c & e)	255	SBP_Change	252	-2.58	12.51	0.79	-2	-44	60
		DBP_Change	252	-1.53	8.30	0.52	-1.00	-25.00	24.00
		BMI_Change	246	-0.5	0.78	0.05	-0.46	-3.84	1.38
		24-hour_urine_sodium_Change	241	-49.15	62.06	4.00	-47.04	-353.08	138.04
Combined intervention (subset a)	112	SBP_Change	111	-4.41	15.29	1.45	-4	-64	28
		DBP_Change	111	-2.84	9.84	0.93	-2.00	-31.00	22.00
		BMI_Change	105	-1.36	1.08	0.11	-1.29	-4.21	1.38
		24-hour_urine_sodium_Change	108	-35.78	62.14	5.98	-27.65	-183.14	98.64
All sodium reduction (subsets a & c & e)	367	SBP_Change	363	-3.14	13.42	0.70	-3	-64	60
		DBP_Change	363	-1.93	8.80	0.46	-2.00	-31.00	24.00
		BMI_Change	351	-0.76	0.96	0.05	-0.61	-4.21	1.38
		24-hour_urine_sodium_Change	349	-45.02	62.30	3.33	-44.38	-353.08	138.04
All weight loss (subsets a & b)	224	SBP_Change	221	-3.86	14.38	0.97	-4	-64	46
		DBP_Change	221	-1.79	10.15	0.68	-2.00	-31.00	58.00
		BMI_Change	211	-1.45	1.06	0.07	-1.37	-5.01	1.38
		24-hour_urine_sodium_Change	210	-21.67	64.01	4.42	-17	-186.95	132.58
ALL	722	SBP_Change	706	-2.36	13.16	0.50	-2	-64	60
		DBP_Change	706	-1.30	8.74	0.33	-1.00	-31.00	58.00
		BMI_Change	674	-0.65	1.02	0.04	-0.5	-5.01	1.7
		24-hour_urine_sodium_Change	665	-27.66	64.85	2.51	-25.3	-353.08	138.04

Table S3. Associations of gene polymorphisms with the relationship of DBP change vs. BMI and 24-hour sodium change\*

Group	Polymorphism	Na + Wt		Wt Only		Na Only		Polymorphism		Na + Wt + Investigator-Selected		Wt Only + Investigator-Selected		Na Only + Investigator-Selected	
		One	All	One	All	One	All	One	All	One	All	One	All	One	All
Group 1: Control	rs4646994	0.093						rs2820037	0.017	0.021	0.010	0.015	0.018	0.021	
	rs2820037	0.060	0.071	0.032	0.040	0.058	0.069	rs7961152	0.082	0.080	0.091	0.091	0.080	0.084	
	rs1799983	0.087		0.091		0.092		rs1799983	0.061		0.051		0.067		
	rs6997709	0.070	0.027			0.068	0.028	rs6997709		0.065			0.067	0.071	
Group 2: Wt Only	rs4646994	0.004	0.006	0.012	0.011	0.005	0.006	rs4646994	0.007	0.010	0.019	0.019	0.008	0.010	
	rs4961	0.023		0.028		0.027		rs4961	0.032		0.035	0.097	0.034		
	rs5370		0.039	0.091	0.019		0.041	rs5186	0.099	0.012	0.065	0.004	0.050	0.012	
	rs1982073	0.038		0.023		0.044		rs1982073	0.046		0.028		0.050		
	rs2820037	0.004	<0.001	0.002	<0.001	0.005	<0.001	rs2820037	0.002	0.001	0.001	<0.001	0.002	0.001	
	rs1800896		0.056	0.092	0.019		0.058	rs1800896				0.065		0.004	
	rs5744292	<0.001	0.002	<0.001	0.002	<0.001	0.003	rs5744292	<0.001	0.005	<0.001	0.003	<0.001	0.004	
	rs4684847	0.009	0.009	0.003	0.005	0.011	0.010	rs4684847	0.018	0.042	0.006	0.020	0.019	0.040	
rs1799983	0.020		0.023		0.023		rs1799983	0.019		0.023		0.021			
Group 3: Na Only	rs5443	0.053	0.046	0.048	0.047	0.053	0.047	rs4961	0.073	0.045	0.065	0.037	0.072	0.047	
	rs1982073	0.056	0.086	0.035	0.054	0.056	0.087	rs5443	0.072	0.071	0.064	0.075	0.071	0.073	
	rs7961152		0.063		0.056		0.064	rs1982073	0.058		0.035	0.074	0.058		
	rs1937506	0.092		0.082		0.092		rs7961152	0.012	0.005	0.011	0.004	0.012	0.005	
Group 4: Both Na+Wt	rs4646994	0.092	0.097	0.053	0.071	0.095		rs1937506	0.070	0.070	0.062	0.004	0.070		
	rs2820037	0.026	0.051	0.033	0.071	0.023	0.055	rs2820037	0.031	0.081	0.035	0.076	0.029	0.069	
	rs5744292	0.008	0.002	0.010	0.007	0.011	0.003	rs5744292	0.025	0.024	0.029	0.068	0.032	0.024	
	rs11110912	0.086		0.039	0.093	0.067		rs11110912	0.067	0.067	0.026	0.067	0.053		
rs1800629		0.045				0.059	rs1800872	0.076		0.082		0.079			

Group 5:	rs4646994	0.097	0.095	0.092	0.091		rs4646994	0.074	0.077	0.080	0.083	0.095	0.099
All Na	rs5370	0.033	0.037			0.033	rs5370	0.045	0.067			0.045	0.064
	rs5443	0.032	0.023	0.078	0.083	0.034	rs1982073	0.056		0.034	0.049	0.069	
	rs1982073	0.049	0.068	0.031	0.036	0.060	rs1800896	0.086	0.059	0.045	0.025	0.077	0.055
	rs1800896				0.067		rs7961152	0.034	0.021	0.015	0.006	0.041	0.026
	rs5744292	0.005	0.004	0.006	0.010	0.006	rs5744292	0.013	0.023	0.014	0.040	0.015	0.027
	rs1937506	0.078	0.079	0.098	0.095		rs11110912				0.083		
	rs11110912	0.094	0.067	0.062	0.025	0.085							
Group 6:	rs4646994	0.080	0.080				rs4646994	0.052	0.053				
All Wt	rs5186	0.079		0.077		0.077	rs5186	0.030	0.047	0.025	0.037	0.031	0.041
	rs1982073	0.059	0.039	0.049	0.043	0.079	rs1982073	0.070	0.079	0.054	0.069	0.095	0.097
	rs2820037	0.005	<0.001	0.002	<0.001	0.006	rs2820037	0.003	<0.001	0.001	<0.001	0.004	<0.001
	rs5744292	<0.001	0.003	0.001	0.005	0.001	rs5744292	0.001	0.019	0.003	0.031	0.002	0.021
	rs4684847	0.098		0.057			rs4684847	0.090		0.050	0.076		
	rs11110912	0.027	0.020	0.004	0.006	0.022	rs11110912	0.018	0.013	0.002	0.003	0.015	0.007
Group 7:	rs4646994	0.053	0.056	0.051	0.051	0.073	rs4961	0.011	0.007	0.009	0.006	0.012	0.008
All	rs4961				0.089		rs1982073	0.018	0.019	0.010	0.010	0.026	0.027
	rs5443	0.066	0.052			0.071	rs1800896	0.053	0.035	0.029	0.016	0.048	0.033
	rs1982073	0.038	0.040	0.028	0.027	0.050	rs5744292	0.071	0.086			0.071	0.086
	rs1800896		0.067	0.052	0.028	0.097	rs1937506			0.089		0.071	0.086
	rs5744292	0.081	0.062			0.083	rs11110912		0.085		0.029		0.074
	rs1937506			0.092	0.085								
	rs11110912				0.034	0.090							

\* Changes between baseline and first drug withdrawal visit for DBP and BMI and between baseline and 9-month visit for 24-hour sodium.

The table includes polymorphisms that were associated ( $p < 0.1$ ) with weight and salt sensitivity using linear statistics as described in detail on page 6.

### **Example Calculations for Tables S4 and S5**

Tables S4 and S5 depict the estimation of the number of truly significant observed associations (true discoveries) as the number of observed significant associations minus the number of false discoveries expected to occur at a given P value based on our simulation data. Tables S4 and S5 show the 50th and 80th percentiles of counts of false discoveries generated from 100 simulations of the random data set for SBP (Table S4) and 100 simulations for DBP (Table S5) (see pages 11-12 of the manuscript for further details). As an example, in Table S4, Group 2 (Wt Only), the difference between the expected discoveries (at the 50th percentile, with  $\alpha=0.1$ ) and the observed discoveries ranges between 1 and 3.5. This suggests that the number of true discoveries would be 2 or 3. In Table 2, we ranked the observed six polymorphisms with significant association to SBP change according to the P values of the association and chose the 3 polymorphisms with the lowest p-values. Those were included in the third column of Table 3. Similar estimations were performed for DBP change as shown in Tables S5, S3, and 3, respectively.

Table S4. False and observed discoveries of polymorphisms that intervene in the relationship of SBP change with BMI change

Group	Expected Number of False Discoveries	Number of Observed Statistically Significant Discoveries											
		$\alpha=0.1$		$\alpha=0.05$		$\alpha=0.01$		80%		80%		obs	
		50%	80%	50%	80%	50%	80%	obs	50%	80%	obs	80%	obs
<b>Group 1: Control</b>													
	6	1	2	0	1	0	1	1	0	0	0	0	0
	5	1	2.2	1	1.2	1	1	1	0	0	0	0	0
	4	2	3	1	2	1	2	2	0	0	1	0	1
	3	2	3.2	1	2	1	2	2	0	1	1	1	1
	2	3	4	1	3	1	3	2	0	1	1	1	1
	1	3	5	1	3	1	3	3	0	1	1	1	1
<b>Group 2: Wt Only</b>													
	6	1	2	0	1	0	1	2	0	0	0	0	0
	5	1	2	1	1	1	1	2	0	0	0	0	0
	4	2	2	1	1	1	1	2	0	1	0	1	0
	3	2.5	4	1	2	1	2	2	0	1	1	1	1
	2	3	5	1	3	1	3	2	0	1	2	1	2
	1	4	5	2	3	2	3	3	0	1	2	1	2
<b>Group 3: Na Only</b>													
	6	1	3	0	1	0	1	1	0	0	0	0	0
	5	1	3	0	1	0	1	1	0	0	1	0	1
	4	2	3	1	2	1	2	1	0	0	1	0	1
	3	2	4	1	2	1	2	2	0	1	1	1	1
	2	2	4	1	2.2	1	2.2	3	0	1	1	1	1
	1	3	4	1	3	1	3	4	0	1	1	1	1
<b>Group 4: Both Na+Wt</b>													
	6	1	2	0	1	0	1	2	0	0	0	0	0
	5	1	2	0	1	0	1	2	0	0	0	0	0
	4	1	2	0	1	0	1	2	0	0	0	0	0
	3	2	4	1	2	1	2	2	0	1	1	1	1
	2	3	5	1	3	1	3	2	0	1	1	1	1
	1	4	5	2	3	2	3	2	0	1	1	1	1
<b>Group 5: All Na</b>													
	6	1.5	2	0	1	0	1	2	0	0	1	0	1
	5	2	3	1	1	1	1	3	0	0	1	0	1
	4	2	3	1	2	1	2	4	0	0	1	0	1
	3	2	3	1	2	1	2	5	0	1	2	1	2
	2	3	4	1	2.2	1	2.2	5	0	1	2	1	2
	1	3	4	2	3	2	3	7	0	1	2	1	2

Group 6: All Wt	6	1	2	2	0	1	2	0	0	1
	5	1	3	2	1	2	2	0	0	1
	4	2	3	3	1	2	2	0	0	1
	3	2.5	4	5	1	2	2	0	1	1
	2	3	5	5	2	3	2	0	1	1
	1	4	5	5	2	3	5	0	1	1
Group 7: All	6	1	2	5	0	1	2	0	0	0
	5	1	3	5	1	1	3	0	0	0
	4	2	3	5	1	2	3	0	0	0
	3	2	3	5	1	2	3	0	1	0
	2	2	4	7	1	2	6	0	1	0
	1	3	4	8	2	3	7	0	1	0

50%=Median Number of False Discoveries, 80%=80th% of False Discoveries, obs=Number of actual discoveries from the data

\* Changes between baseline and first drug withdrawal visit for SBP and BMI and between baseline and 9-month visit for 24-hour sodium



Table S5. False and observed discoveries of polymorphisms that intervene in the relationship of DBP change with BMI change

Group	Expected Number of False Discoveries	Number of Observed Statistically Significant Discoveries											
		$\alpha=0.1$		$\alpha=0.05$		$\alpha=0.01$		80%		50%		80%	
		50%	80%	obs	50%	80%	obs	50%	80%	obs	50%	80%	obs
Group 1: Control	6	1	2	1	0	1	0	0	1	0	0	0	0
	5	1	2	1	1	1	0	0	1	0	0	0	0
	4	2	3	1	1	2	1	0	2	1	0	1	0
	3	2	4	3	1	2	1	0	2	1	0	1	0
Group 2: Wt Only	2	3	5	4	2	3	1	0	3	1	0	1	0
	1	4	6	4	2	3	2	1	3	2	1	1	0
	6	2	3	1	1	2	1	0	2	1	0	0	0
	5	2	4	2	1	2	2	0	2	2	0	1	0
Group 3: Na Only	4	3	4	3	2	2	2	0	2	2	0	1	0
	3	4	6	5	2	4	3	1	4	3	0	1	1
	2	5	7	6	3	5	3	1	5	3	1	2	1
	1	7	9	6	4	6	4	1	6	4	1	2	2
Group 4: Both Na+Wt	6	1	3	1	1	2	0	0	2	0	0	0	0
	5	2	3	2	1	2	0	0	2	0	0	0.2	0
	4	2	3	3	1	2	0	0	2	0	0	1	0
	3	3	5	4	2	3	1	0	3	1	0	1	0
Group 5: All Na	2	4	5	5	2	3	2	0	3	2	0	1	0
	1	5	6	5	3	4	3	1	4	2	1	2	1
	6	1	2	2	1	1	1	0	1	1	0	0	0
	5	2	3	2	1	2	1	0	2	1	0	0	0
Group 5: All Na	4	3	5	6	1	3	1	0	3	1	0	1	0
	3	4	5	7	2	3.2	2	1	4	2	1	1	1
	2	5	6	9	3	4	5	1	4	5	1	2	1
	1	5.5	7	9	3	5	6	1	5	6	1	2	1

Group 6: All Wt	6	2	3	3	1	2	3	0	1	1
	5	3	4	3	1.5	3	3	0	1	1
	4	4	5	3	2	3	3	0	1	1
	3	4	6	4	3	4	3	1	1	1
	2	5	7.2	5	3	5	3	1	2	1
	1	7	9	6	4.5	6.2	4	2	3	2
Group 7: All	6	1.5	3	0	0	1.2	0	0	0	0
	5	2	3	1	1	2	0	0	0.2	0
	4	2	4	1	1	3	0	0	1	0
	3	3	5	3	2	3	0	0	1	0
	2	4	6	6	2	4	2	0	1	0
	1	5	7	8	3	5	3	0	2	1

50%=Median Number of False Discoveries, 80%=80th% of False Discoveries, obs=Number of actual discoveries from the data

\* Changes between baseline and first drug withdrawal visit for DBP and BMI and between baseline and 9-month visit for 24-hour sodium



Table S7. Results of the recursive partitioning model for SBP and DBP

SBP					
Subset	Slope	Group size	T	P value	Polymorphisms
1	-2.94651014	46	-2.338325835	0.009685176	rs5370#2 & rs699#2 & rs1982073#2
1	-14.41029055	13	-2.34445042	0.009527572	rs5370#2 & rs699#2 & rs1982073#2 & rs5443=1
1	7.667375757	19	1.471228419	0.070614677	rs5370=2 & rs1800896#2 & rs7961152=1
2	5.547568816	50	2.266161648	0.011720744	rs4646994#1 & rs1800629=1
2	6.016794643	41	2.473142892	0.006696529	rs4646994#1 & rs1800629=1 & rs1982073#1
2	6.506129447	31	1.73851433	0.041060114	rs4646994#1 & rs1800629=1 & rs1982073#1 & rs1800896#1
3	-0.13439452	57	-3.198217793	0.000691399	rs1800896=2 & rs1799983#1
3	0.041535486	77	2.684618183	0.003630635	rs1800896#2 & rs1982073#3
3	0.05390639	29	2.373680826	0.008805884	rs1800896#2 & rs1982073=2 & rs1799983=1
4	11.38697663	9	1.147339669	0.125620633	rs6997709#2 & rs1937506=1 & rs1982073=1
4	1.341591295	29	-0.308635249	0.378799502	rs6997709#2 & rs1937506#1
5	-0.090565882	82	-3.38517753	0.000355661	rs1937506#1 & rs4646994#2
5	0.141832875	35	2.694693959	0.003522665	rs1937506#1 & rs4646994=2 & rs7961152=2
5	-0.10229772	48	-3.022753044	0.001252433	rs1937506=1 & rs1800629=2
6	6.860829769	33	2.141618685	0.016112089	rs699#1 & rs4961=2
6	0.698090431	49	-1.3147861	0.0942909	rs699#1 & rs4961#2 & rs1937506#1
7	5.626374158	42	2.581514081	0.004918399	rs1800872=2 & rs5186=1 & rs1800796=1 & rs7961152#1 & rs699#1
7	-0.904445516	44	-1.791633824	0.036595821	rs6997709#1 & rs187238#1 & rs5186#1 & rs1800796=1 & rs7961152#1 & rs699#1
DBP					
Subset	Slope	Group size	T	P value	Polymorphisms
1	-1.88455052	40	-2.77716966	0.002741727	rs5370#2 & rs4646994#1 & rs1982073#2 & rs699#1
1	7.109257428	20	2.056431449	0.019870474	rs699=1 & rs1982073=2 & rs7961152#2
2	-0.568763615	20	-2.47064874	0.006743411	rs5443=1 & rs1982073#1 & rs1800795#2
2	3.866313665	44	1.629377609	0.051616553	rs1800795=2
3	0.042142575	47	2.495508904	0.00628883	rs1800896#2 & rs1982073#3 & rs5186=2
3	-0.043398761	130	-3.188426683	0.000715246	rs1800896=2
3	-0.053282823	69	-2.613497038	0.004481043	rs1800896=2 & rs1982073#2
3	-0.133780601	18	-3.099135341	0.000970432	rs1800896=2 & rs1982073#2 & rs7961152=1
4	5.150537534	14	2.416763396	0.007829596	rs1937506=1 & rs1982073=1
4	-1.375319427	52	-3.424850556	0.000307569	rs1937506=1 & rs1982073#1
4	-2.841602813	27	-3.508116081	0.000225646	rs1937506=1 & rs1982073#1 & rs5186=2
5	0.044072794	70	3.426886035	0.000305273	rs1800896#3 & rs5443#3 & rs1800872#2 & rs1800795#2
5	-0.03596774	53	-1.995808429	0.022977389	rs1800896#3 & rs5443#3 & rs1800872#2 & rs1800795=2
5	-0.04712368	57	-2.691681112	0.003554644	rs1800896#3 & rs5443=3
6	3.303274366	73	1.872977184	0.030535768	rs4961#2 & rs5443#3 & rs1982073#2

7	3.125770798	199	3.197938477	0.000692069	rs11110912=1 & rs4646994#2 & rs699#3
7	4.163061022	77	2.78698206	0.002660071	rs11110912=1 & rs4646994#2 & rs699#3 & rs5443#1 & rs1982073#2
7	0.015813674	270	-3.663384585	0.000124452	rs11110912=1 & rs4646994=2
7	-1.233170397	67	-2.919642028	0.001752168	rs11110912=1 & rs4646994=2 & rs1982073#3 & rs1937506#1
7	-0.221304402	105	-2.529442835	0.005712189	rs11110912=1 & rs4646994=2 & rs1982073=3

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## Figure Legends

Figure S1. Box plots of weight sensitivity and salt sensitivity associated with selected polymorphisms.

Figure S2. Diagram of a recursive partition tree with polymorphisms as the partitioning variables in the weight loss group.

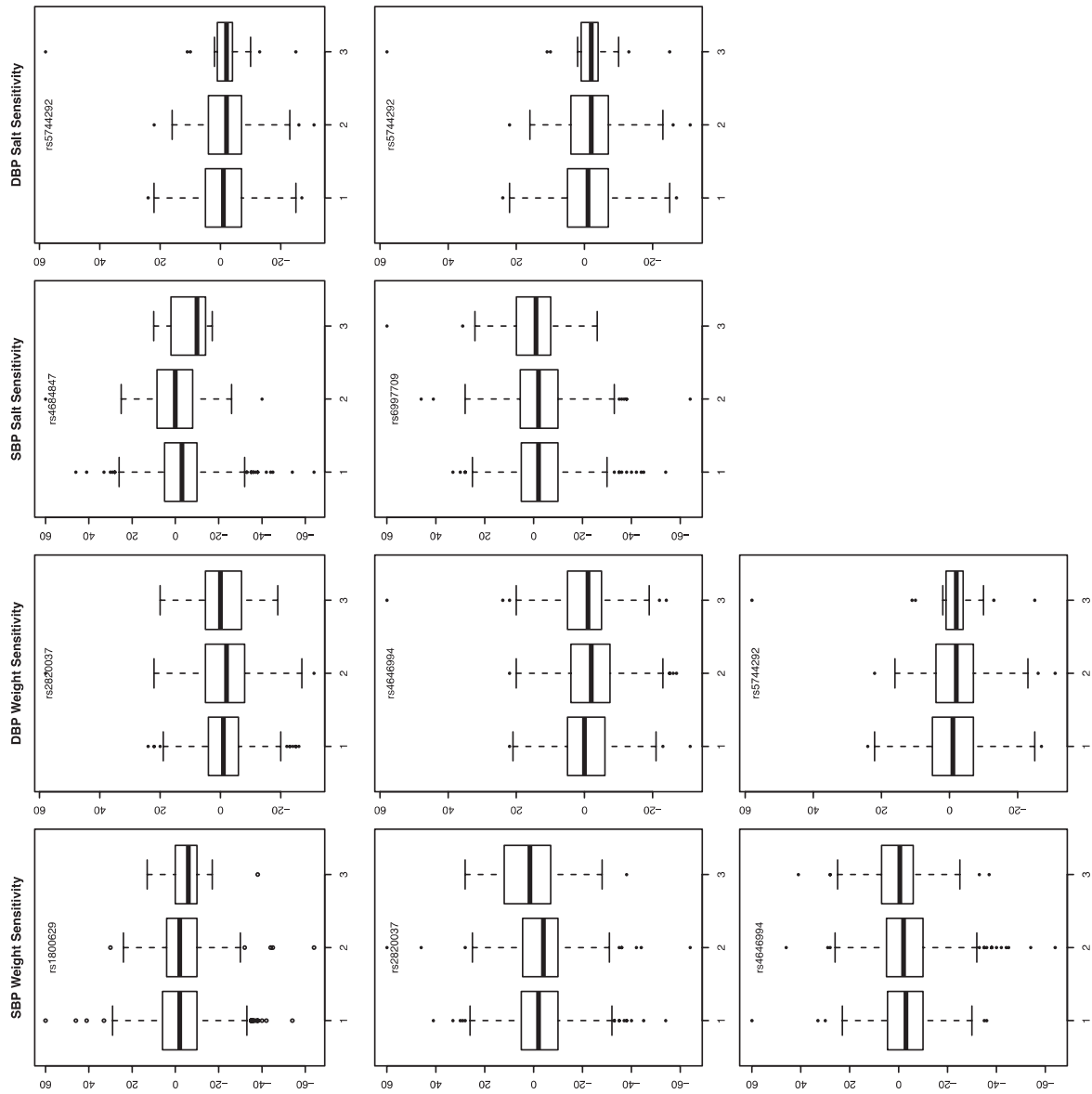


Figure S1.

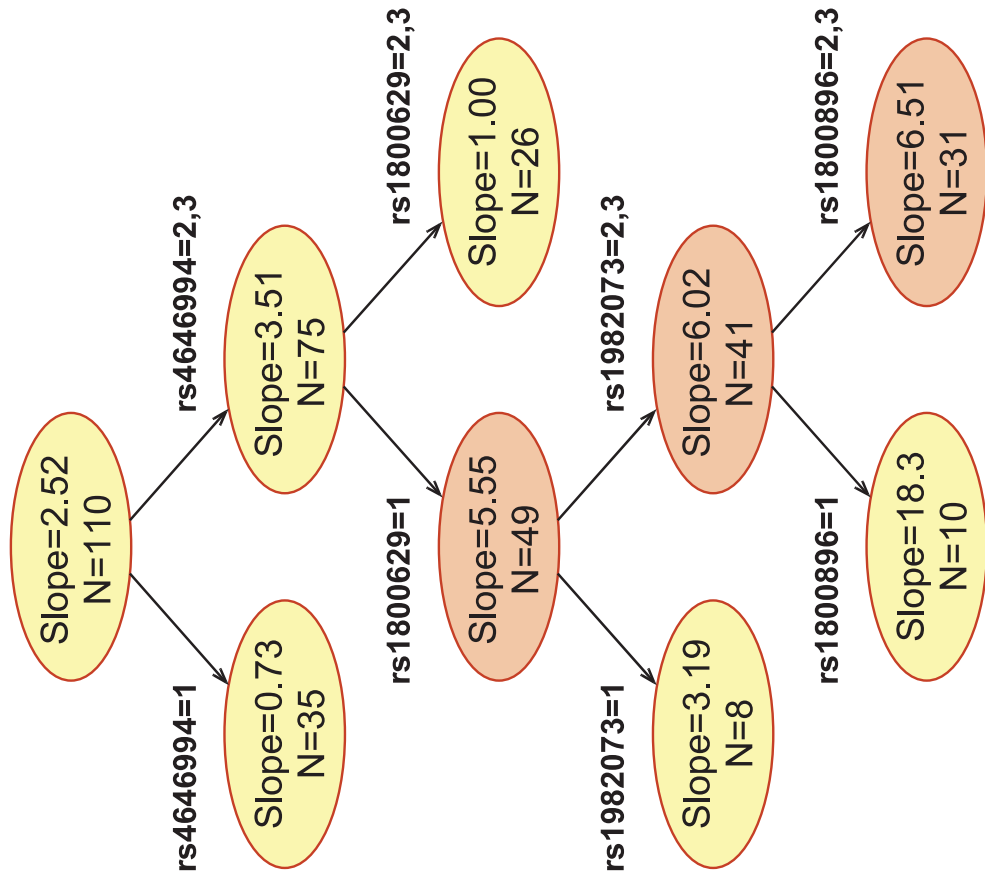


Figure S2.