

## Genetic variation at the delta-sarcoglycan (*SGCD*) locus elevates heritable sympathetic nerve activity in human twin pairs.

Hightower *et al.*, 05/28/13

### ONLINE TABLES AND TABLE LEGENDS SUPPLEMENT.

**Table S1.** Heritability ( $h^2$ ), shared genetic determination (genetic co-determination,  $RhoG$  also known as pleiotropy,  $\rho_G$ ) and environmental determination (environmental co-determination,  $RhoE$ ,  $\rho_E$ ) for traits correlated with plasma norepinephrine (pNE), by variance component analyses in twin pairs.  $RhoG$  and  $RhoE$  are fractions (covariances), scaled from -1 to +1, and determined in SOLAR. Pearson parametric trait-on-trait correlations are also reported. BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LV, left ventricular; SVR, systemic vascular resistance; CHGB, chromogranin B; eGFR, estimated glomerular filtration rate; eGFR (CKD-EPI), estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration algorithm. Significant differences ( $P < 0.05$ ) are **bold**. Analyses were completed in monozygotic and dizygotic twin pairs.

**Table S2.** Norepinephrine secretion quantiles, with quantile-associated traits: Descriptive and inferential statistics for twin and sibling study populations, divided about the median value for plasma norepinephrine. Inferential statistics for twins were derived from GEE to account for correlations within pairs. Numbers (N) describe the number of individuals analyzed. CHGB indicates Chromogranin B; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; Lp(a), Lipoprotein (a); eGFR (CKD-EPI), estimated glomerular filtration rate by Chronic Kidney Disease-Epidemiology Collaboration algorithm. Significant differences ( $P < 0.05$ ) are **bold**.

**Table S3.** *SGCD* genetic variation: Prediction of multiple trait values by the peak norepinephrine secretion-associated *SGCD* SNP (rs1835919) in twins and siblings. An analysis of subject's genotype that compares pleiotropic effects across physical, physiological, and biochemical traits. Subjects are analyzed by an additive model for single nucleotide polymorphism (SNP) resulting disease phenotypes. Numbers (N) describe the number of individuals analyzed. Significant differences ( $P < 0.05$ ) are in **bold**. FDR indicates false discovery rate; CHGB, Chomogranin B; FFA, free fatty acid.

Table S1. Plasma norepinephrine (pNE): Heritable shared genetic and environmental effects in physical, hemodynamic/autonomic, and biochemical traits.												
Traits	Heritability			Correlation (Pearson) with pNE		N	Genetic codetermination with pNE			Environmental codetermination with pNE		
	h <sup>2</sup>	SEM	p	Correlation Coefficient	Sig. (2-tailed)		RhoG	SEM	p	RhoE	SEM	p
<b>Physical</b>												
BMI	0.813	0.028	<b>3.67E-33</b>	0.03	0.501	521	-0.078	0.087	<b>3.70E-01</b>	-0.082	0.092	0.378
<b>Hemodynamic/Autonomic</b>												
SBP, mmHg	0.446	0.067	<b>1.60E-08</b>	0.124	<b>6.00E-03</b>	493	0.004	0.119	0.971	0.064	0.091	0.483
DBP, mmHg	0.440	0.071	<b>1.00E-07</b>	0.119	<b>8.00E-03</b>	495	-0.080	0.124	0.515	0.200	0.095	<b>4.20E-02</b>
HR,beats/min	0.622	0.053	<b>1.84E-15</b>	-0.050	0.257	507	-0.066	0.104	0.527	0.074	0.097	0.454
LV contractility, mmHg/s	0.399	0.072	<b>9.00E-07</b>	-0.044	0.330	491	0.071	0.125	0.572	-0.064	0.096	0.507
Cardiac output, l/min	0.668	0.048	<b>7.38E-18</b>	-0.015	0.743	485	-0.148	0.099	0.138	0.022	0.103	0.829
Cardiac index, l/min/m <sup>2</sup>	0.604	0.056	<b>2.13E-14</b>	-0.029	0.529	488	-0.075	0.106	0.479	0.072	0.103	0.485
Stroke volume, ml/m <sup>2</sup>	0.731	0.041	<b>2.19E-21</b>	-0.007	0.881	487	-0.069	0.095	0.473	-0.167	0.100	0.103
Stroke volume index, ml	0.582	0.058	<b>6.38E-13</b>	-0.018	0.690	487	-0.019	0.108	0.861	-0.092	0.100	0.362
Systemic vascular compliance, ml/mmHg	0.533	0.063	<b>6.40E-11</b>	-0.118	<b>9.00E-03</b>	491	-0.222	0.108	<b>4.42E-02</b>	-0.068	0.097	0.482
SVR, dynes/s/cm <sup>5</sup>	0.573	0.056	<b>1.18E-13</b>	0.095	<b>3.60E-02</b>	491	0.200	0.106	<b>6.20E-02</b>	0.005	0.100	0.963
Baroreceptor slope upward deflection, msec/mmHg	0.254	0.083	<b>1.91E-03</b>	-0.153	<b>4.74E-04</b>	517	0.100	0.161	0.529	-0.151	0.092	0.106
Baroreceptor slope downward deflection, msec/mmHg	0.370	0.075	<b>6.30E-06</b>	-0.118	<b>8.00E-03</b>	507	0.078	0.128	0.540	-0.105	0.097	0.284
<b>Biochemical:</b>												
<b>Catecholamines</b>												
Plasma norepinephrine, pg/ml	0.652	0.050	<b>3.19E-16</b>	-	-	-	-	-	-	-	-	-
Plasma epinephrine, pg/ml	0.665	0.051	<b>5.09E-16</b>	0.226	<b>1.82E-07</b>	523	0.355	0.086	<b>2.56E-04</b>	0.273	0.087	<b>3.00E-03</b>
Urine norepinephrine, ng/g	0.490	0.074	<b>1.00E-07</b>	0.413	<b>6.42E-19</b>	425	0.062	0.097	0.527	0.219	0.092	<b>2.10E-02</b>
Urine epinephrine, ng/g	0.781	0.035	<b>2.16E-24</b>	0.062	0.208	419	0.430	0.102	<b>3.38E-04</b>	0.294	0.089	<b>2.00E-03</b>
CHGB [312-331], nmol/l	0.565	0.056	<b>1.11E-13</b>	0.120	<b>8.00E-03</b>	494	0.298	0.100	<b>4.58E-03</b>	0.057	0.087	0.517
CHGB [439-451], nmol/l	0.476	0.067	<b>3.98E-09</b>	0.004	0.936	498	0.124	0.123	0.319	0.088	0.092	0.345
<b>Renin-angiotensin system</b>												
Plasma active renin pg/ml	0.524	0.062	<b>2.70E-11</b>	-0.128	<b>1.5E-02</b>	360	-0.243	0.112	<b>3.19E-02</b>	0.096	0.090	0.289
<b>Metabolic</b>												
Uric acid plasma, mg/dl	0.647	0.055	<b>1.28E-14</b>	0.025	0.586	488	0.100	0.104	0.341	-0.146	0.092	0.120
Plasma free fatty acids, mmol/l	0.275	0.084	<b>1.02E-03</b>	0.117	<b>1.40E-02</b>	438	-0.065	0.161	0.684	0.168	0.090	<b>6.70E-02</b>
Ratio urine to plasma uric acid	0.376	0.075	<b>6.40E-06</b>	0.007	0.877	486	-0.038	0.131	0.773	0.017	0.091	0.850
Plasma neuropeptide Y, pmol/L	0.727	0.037	<b>1.29E-25</b>	0.177	<b>6.01E-05</b>	369	0.151	0.088	0.093	0.167	0.088	0.065
<b>Renal traits</b>												
eGFR (CKD EPI), ml/min/1.73m <sup>2</sup>	0.673	0.047	<b>3.80E-18</b>	-0.272	<b>8.97E-10</b>	492	-0.507	0.090	<b>1.99E-07</b>	0.283	0.083	<b>1.42E-03</b>

Table S2. Plasma norepinephrine quantiles: Effects on demographic, physical, and physiological traits							
Traits	pNE <305.8 pg/ml			pNE ≥305.8 pg/ml			Significance (2-tailed)
	N	Mean	SEM	N	Mean	SEM	
<b>Demographic</b>							
Age, years	266	36.11	0.892	265	42.42	1.025	<b>4.29E-06</b>
Sex, M/F	266	65/201		265	87/178		<b>3.20E-02</b>
Blood pressure status, NT/HTN (%)	266	250(94%)/16(6%)		265	228(86%)/37(14%)		<b>2.00E-03</b>
<b>Physical</b>							
Body mass index, kg/m <sup>2</sup>	261	25.33	0.291	260	25.32	0.301	0.970
<b>Physiological</b>							
<b>Hemodynamic</b>							
Systolic blood pressure, mmHg	250	121.9	0.759	248	124.9	0.825	<b>6.00E-03</b>
Diastolic blood pressure, mmHg	252	75.2	0.532	247	77.0	0.615	<b>2.60E-02</b>
Mean arterial pressure, mmHg	254	89.4	0.632	249	91.2	0.663	<b>4.90E-02</b>
Pulse pressure, mmHg	253	57.8	0.656	247	59.6	0.632	<b>4.30E-02</b>
Heart rate, beats/min	255	70.1	0.670	252	68.3	0.660	<b>5.50E-02</b>
Left ventricular contractility, mmHg/s	249	1181.4	11.183	241	1208.3	12.387	0.107
Cardiac output, l/min	245	4.9	0.069	240	4.8	0.069	0.577
Cardiac index, l/min/m <sup>2</sup>	247	2.8	0.031	241	2.7	0.032	0.235
Stroke volume, ml	247	70.0	0.823	240	70.3	0.799	0.841
Stroke volume index, ml/m <sup>2</sup>	248	39.5	0.276	239	39.4	0.283	0.863
Systemic vascular compliance, ml/mmHg	248	1.3	0.014	243	1.2	0.015	<b>6.20E-02</b>
Systemic vascular resistance, dynes/s/cm <sup>5</sup>	249	1490.8	19.986	242	1544.9	19.956	<b>5.60E-02</b>
Brachial artery compliance, ml/mmHg	247	0.1	0.001	240	0.1	0.002	0.956
<b>Autonomic</b>							
Baroreceptor slope upward deflection, msec/mmHg	259	12.8	0.533	258	10.7	0.502	<b>6.00E-03</b>
Baroreceptor slope downward deflection, msec/mmHg	255	10.2	0.428	252	8.9	0.382	<b>2.40E-02</b>
<b>Biochemical: Catecholamines</b>							
Plasma norepinephrine, pg/ml	266	214.1	3.448	265	442.3	7.193	<b>1.18E-109</b>
Plasma epinephrine, pg/ml	264	23.7	0.938	259	30.5	1.217	<b>1.08E-05</b>
Plasma dopamine, pg/ml	260	17.8	1.739	262	21.7	1.200	<b>6.50E-02</b>
Urine norepinephrine, ng/g	218	241.0	6.468	207	320.1	8.601	<b>7.94E-13</b>
Urine epinephrine, ng/g	216	122.5	3.863	203	122.2	3.664	0.956
Urine dopamine, ng/g	219	1663.2	45.853	209	1589.9	35.807	0.211
CHGB [312-331], nmol/l	256	0.8	0.018	238	0.8	0.022	<b>7.70E-02</b>
CHGB [439-451], nmol/l	258	0.3	0.008	240	0.3	0.009	0.862
<b>Biochemical: renin-angiotensin system (RAS)</b>							
Plasma active renin, pg/ml	194	16.5	0.814	166	14.0	0.714	<b>2.50E-02</b>
Plasma aldosterone, pg/ml	238	124.3	4.331	219	133.23	4.568	0.156

Urine aldosterone, pg/g	130	3.2	0.192	160	3.00	0.143	0.462
<b>Biochemical: Metabolic</b>							
Glucose plasma, mg/dl	256	80.48	0.612	236	81.18	0.730	0.459
Plasma QUICKI index	221	0.34	0.002	204	0.341	0.002	0.195
Plasma insulin, uUnit/ml	243	11.29	0.429	239	10.30	0.363	<b>8.40E-02</b>
Uric acid plasma, mg/dl	254	4.13	0.061	234	4.18	0.073	0.565
Ratio urine to plasma uric acid	248	6.61	0.287	217	7.79	0.540	<b>4.80E-02</b>
Plasma FFA, mmol/l	233	0.48	0.016	205	0.53	0.015	<b>3.80E-02</b>
Plasma leptin, ng/mL	189	9.65	0.569	185	7.84	0.422	<b>1.20E-02</b>
P Selectin, ng/mL	197	83.61	2.932	183	111.12	4.71	<b>5.33E-09</b>
Total cholesterol, mg/dl	188	168.74	2.632	186	181.82	2.425	<b>2.95E-04</b>
Triglycerides, mg/dl	182	69.93	2.83	182	84.55	2.95	<b>1.00E-3</b>
HDL, mg/dl	187	65.19	2.151	184	60.92	1.860	0.134
LDL, mg/dl	188	100.03	2.033	184	107.88	2.171	<b>9.00E-03</b>
Lp( a), mg/dl	127	4.24	0.233	155	5.04	0.233	<b>1.90E-02</b>
Plasma neuropeptide Y, pmol/L	258	71.32	1.896	252	82.02	2.009	<b>1.20E-04</b>
<b>Biochemical: Renal</b>							
eGFR (CKD EPI), ml/min/1.73m <sup>2</sup>	258	105.13	1.340	234	93.78	1.422	<b>1.10E-08</b>

Table S3: *SGCD* genotype-specific analysis: A comparison of pleiotropic effects across physical, physiological, and biochemical traits.

Phenotype	SGCD Merlin p	FDR	Model: Additive			
			Genotype	N	Mean	SEM
<b>Physical</b>						
Body mass index, kg/m <sup>2</sup>	<b>0.0158</b>	<b>0.0237</b>	A/A	396	25.52	0.297
			G/A	174	24.64	0.378
			G/G	26	23.86	1.278
<b>Physiological</b>						
Brachial artery compliance, ml/mmHg	<b>0.0179</b>	<b>0.0179</b>	A/A	365	7.24E-02	0.001
			G/A	163	6.96E-02	0.001
			G/G	24	6.92E-02	0.003
Cardiac output, ml/mmHg	0.2433	0.1123				
Heart rate, beats/min	0.2569	0.1101	A/A	380	69.98	0.652
			G/A	167	68.09	0.953
			G/G	27	70.00	2.481
Systolic blood pressure, mmHg	0.7739	0.3096	A/A	369	123.20	0.662
			G/A	166	122.90	1.016
			G/G	24	127.20	2.931
Diastolic blood pressure, mmHg	0.8427	0.3160	A/A	370	76.00	0.496
			G/A	166	76.26	0.755
			G/G	25	76.54	1.520
Stroke volume index, ml	0.9716	0.3429	A/A	365	39.41	0.279
			G/A	164	39.36	0.386
			G/G	22	39.61	0.669
Systemic vascular compliance, ml/mmHg	<b>0.0131</b>	<b>0.0261</b>	A/A	367	1.26	0.013
			G/A	164	1.21	0.019
			G/G	24	1.19	0.051
Systemic vascular resistance, dynes/s/cm <sup>5</sup>	0.1790	0.0895	A/A	369	1499.00	18.630
			G/A	163	1560.00	24.252
			G/G	24	1463.00	98.668
<b>Biochemical</b>						
CHGB [312-331], nmol/l	0.05889	<b>0.0321</b>	A/A	359	0.86	0.022
			G/A	151	0.94	0.038
			G/G	25	0.96	0.107
CHGB [439-451], nmol/l	<b>0.0173</b>	<b>0.0208</b>	A/A	362	0.33	0.008
			G/A	152	0.36	0.013
			G/G	24	0.34	0.027
Plasma FFA, mmol/l	<b>0.0322</b>	<b>0.0215</b>	A/A	314	0.49	0.013
			G/A	129	0.51	0.021
			G/G	23	0.60	0.072
Plasma norepinephrine, pg/ml	<b>9.89E-06</b>	<b>0.0001</b>	A/A	347	307.30	8.593
			G/A	155	359.80	13.815
			G/G	23	429.00	28.990
Ratio urine to plasma uric acid	<b>0.0130</b>	<b>0.0391</b>	A/A	334	5.63	0.209
			G/A	148	6.58	0.576
			G/G	23	7.94	1.026
Uric acid plasma, mg/dl	<b>0.0348</b>	<b>0.0209</b>	A/A	346	4.19	0.060
			G/A	152	4.07	0.089
			G/G	25	3.91	0.162
Urine norepinephrine, ng/g	<b>0.0296</b>	<b>0.0222</b>	A/A	290	275.33	7.884
			G/A	129	294.93	10.770
			G/G	25	312.01	27.061