

SUPPLEMENTARY DATA

**Modulation of GLP-1 levels by a genetic variant that regulates the cardiovascular effects of intensive glycemic control in ACCORD**

*Shah et al.*

**Supplementary Table S1. Baseline characteristics of entire ACCORD, genetic subset and MIND-MRI biomarker subset**

Characteristic	Whole dataset (N=10,251)	Genotyped dataset (N=8,084)	ACCORD-MIND-MRI Study (N=562)
Female sex, No. (%)	3,952 (38.6)	3,198 (39.6)	262 (46.6)*
Age, mean (SD), y	62.5 (6.7)	62.4 (6.6)	62.8 (5.8)
Whites, No. (%)	6,525 (63.6)	5,311 (65.7)	375 (66.7)*
Diabetes duration, median (IQR), y	10.0 (5.0-15.0)	10.0 (5.0-15.0)	8.0 (5.0-13.0)
Previous cardiovascular event, No. (%)	3,609 (35.2)	2,751 (34.0)	136 (24.2)*
Current Smoker, No. (%)	1,237 (12.1)	958 (11.9)	61 (10.9)
HbA1c, Mean (SD), %	8.3 (1.0)	8.3 (1.0)	8.2 (1.0)
HbA1c, Median (IQR), %	8.1 (7.6-8.9)	8.1 (7.6-8.9)	8.0 (7.5-8.7)
Fasting serum glucose, mean (SD), mg/dl	174.4 (53.4)	175.3 (53.3)	172.8 (52.3)
BMI, mean (SD), kg/m <sup>2</sup>	32.2 (5.4)	32.3 (5.4)	32.7 (5.1)
Waist circumference, mean (SD), cm	106.7 (13.6)	106.8 (13.7)	107.1 (12.9)
Systolic Blood Pressure, mean (SD), mm Hg	136.3 (16.9)	136.2 (17.1)	135.1 (17.1)
Diastolic Blood Pressure, mean (SD), mm Hg	74.8 (10.5)	74.9 (10.7)	74.6 (9.8)
Serum creatinine, mean (SD), mg/dl	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)
<i>Lipids, mean (SD), mg/dl</i>			
Total cholesterol	183.2 (41.2)	183.7 (41.3)	183.9 (40.4)
LDL	104.8 (33.6)	104.9 (33.5)	102.5 (32.8)
HDL, Women	47.0 (12.4)	47.0 (12.5)	48.7 (12.4)
HDL, Men	38.6 (9.5)	38.6 (9.5)	40.1 (9.6)
Triglycerides	188.5 (138.6)	191.1 (144.7)	193.1 (122.9)
<i>Main Glycemia Trial, No. (%)</i>			
Standard	5,123 (50.0)	4,040 (50.0)	295 (52.5)
Intensive	5,128 (50.0)	4,044 (50.0)	267 (47.5)
<i>Blood Pressure Trial, No. (%)</i>			
Standard	2,371 (23.1)	1,852 (22.9)	175 (31.1)
Intensive	2,362 (23.0)	1,818 (22.5)	187 (33.3)
<i>Lipid Trial, No. (%)</i>			
Statin + Placebo	2,753 (26.9)	2,165 (26.8)	102 (18.1)
Statin + Fibrate	2,765 (27.0)	2,249 (27.8)	98 (17.4)

\*Significant difference (p<0.05) between baseline characteristic of MIND sub-study and whole ACCORD study

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Supplementary Table S2. P-values for associations of GRS with baseline and delta (baseline to 12-mth) biomarker levels in ACCORD

Biomarker	Intensive glycemc arm						Standard glycemc arm					
	Baseline*		12months**		delta <sup>§</sup>		Baseline*		12months**		delta <sup>§</sup>	
	beta	P	beta	P	beta	P	beta	P	beta	P	beta	P
Adiponectin	-0.006	0.93	0.002	0.99	-0.007	0.96	0.074	0.51	0.023	0.85	-0.061	0.62
Albumin	-0.010	0.32	-0.007	0.55	0.002	0.87	0.003	0.70	-0.015	0.18	-0.018	0.14
Amylin (Active)	-0.160	0.44	-0.436	0.03	-0.208	0.10	-0.024	0.90	0.227	0.22	0.214	0.11
Amylin (Total)	0.038	0.72	0.057	0.58	0.027	0.79	0.252	0.02	0.277	0.00	0.025	0.70
ApoA1	-0.012	0.55	0.018	0.43	0.027	0.15	-0.008	0.66	-0.008	0.64	0.006	0.62
ApoB	-0.006	0.84	-0.015	0.59	-0.007	0.80	-0.011	0.70	0.010	0.71	0.028	0.19
C-Peptide	0.037	0.54	-0.026	0.74	-0.065	0.32	0.001	0.98	-0.047	0.46	-0.017	0.58
Cystatin-C	0.019	0.42	0.007	0.78	-0.012	0.41	-0.009	0.65	-0.025	0.43	-0.020	0.46
EGF	0.295	0.01	0.110	0.33	-0.182	0.04	0.145	0.12	0.101	0.33	-0.053	0.61
Eotaxin	-0.023	0.71	-0.039	0.55	-0.005	0.88	0.080	0.21	0.060	0.32	-0.014	0.62
Estradiol	-0.038	0.34	-0.029	0.43	0.010	0.78	-0.042	0.14	-0.026	0.32	0.019	0.42
Fractalkine	0.128	0.51	0.038	0.85	-0.048	0.72	0.240	0.19	0.320	0.08	0.078	0.45
Free Fatty Acid	-0.009	0.82	0.018	0.65	0.032	0.50	-0.024	0.55	-0.001	0.98	0.022	0.61
Fructosamine	-0.001	0.95	0.006	0.69	0.010	0.59	0.008	0.60	0.006	0.69	-0.002	0.87
GCSF	-0.038	0.74	-0.100	0.38	-0.005	0.95	-0.104	0.39	-0.178	0.14	-0.053	0.46
GAD-DK	0.767	0.07	-0.128	0.80	-0.282	0.32	0.128	0.76	0.252	0.57	0.315	0.23
GIP	-0.159	0.12	-0.116	0.31	0.008	0.92	0.090	0.27	0.033	0.69	-0.046	0.46
<b>GLP-1 (Active)</b>	<b>0.139</b>	<b>0.19</b>	<b>-0.147</b>	<b>0.16</b>	<b>-0.252</b>	<b>3.0x10<sup>-4</sup></b>	<b>0.025</b>	<b>0.81</b>	<b>0.027</b>	<b>0.78</b>	<b>-0.006</b>	<b>0.93</b>
Ghrelin (Active)	0.177	0.15	0.100	0.42	-0.059	0.51	0.108	0.35	0.200	0.06	0.079	0.28
Glucagon	-0.085	0.70	-0.250	0.28	-0.132	0.42	0.050	0.80	0.199	0.25	0.134	0.21
Glycated Albumin	-0.001	0.96	0.003	0.87	0.009	0.72	0.015	0.39	0.017	0.30	0.004	0.85
Glycoalbumin	-0.011	0.69	0.001	0.96	0.014	0.61	0.019	0.35	-0.036	0.35	-0.054	0.15
HGF	-0.071	0.44	-0.067	0.48	-0.009	0.85	0.073	0.36	0.030	0.70	-0.033	0.41
IFN-γ	0.054	0.75	-0.132	0.45	-0.137	0.13	-0.112	0.50	-0.055	0.73	0.044	0.50
IL-1α	0.030	0.89	-0.094	0.67	-0.110	0.31	0.084	0.67	0.042	0.83	-0.052	0.57
IL-1β	0.012	0.94	-0.119	0.46	-0.090	0.33	0.119	0.41	0.068	0.63	-0.054	0.51
IL-10	0.016	0.92	-0.002	0.99	0.033	0.73	0.196	0.20	0.166	0.22	-0.056	0.52

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IL-12(P40)	-0.026	0.89	-0.129	0.45	-0.044	0.66	0.302	0.06	0.219	0.15	-0.080	0.26
IL-12(P70)	0.029	0.89	-0.134	0.49	-0.129	0.28	0.056	0.75	-0.011	0.94	-0.068	0.50
IL-15	-0.001	0.99	0.071	0.60	0.102	0.18	0.095	0.46	0.137	0.27	0.037	0.62
IL-17	0.092	0.62	-0.183	0.31	-0.233	0.02	-0.117	0.52	-0.087	0.61	0.015	0.84
IL1-ra	0.087	0.54	0.101	0.47	0.009	0.93	0.083	0.59	-0.011	0.94	-0.098	0.20
IL-5	-0.102	0.56	-0.267	0.12	-0.074	0.42	0.229	0.12	0.198	0.18	-0.040	0.54
IL-6	-0.093	0.65	-0.226	0.25	-0.074	0.47	0.079	0.68	-0.002	0.99	-0.088	0.32
IL-8	-0.060	0.62	-0.043	0.72	0.042	0.52	-0.202	0.07	-0.171	0.12	0.005	0.93
IP-10	0.090	0.12	0.083	0.18	-0.003	0.95	-0.004	0.94	-0.044	0.47	-0.049	0.17
Leptin	0.220	0.02	0.218	0.03	0.002	0.98	0.035	0.70	-0.020	0.83	-0.042	0.37
MCP-1	0.006	0.93	0.040	0.51	0.033	0.25	-0.029	0.61	-0.039	0.46	-0.012	0.64
MIF	0.231	0.06	0.114	0.41	-0.120	0.21	0.047	0.64	0.067	0.54	0.031	0.68
MIP-1 $\alpha$	0.095	0.43	0.026	0.84	-0.036	0.58	-0.037	0.77	-0.001	1.00	0.006	0.93
MIP-1 $\beta$	0.075	0.41	0.002	0.98	-0.047	0.39	-0.145	0.16	-0.056	0.53	0.072	0.18
MMP-9	0.015	0.84	-0.011	0.88	-0.034	0.73	0.068	0.42	0.054	0.47	-0.006	0.95
MPO	0.039	0.65	0.048	0.58	0.001	0.99	0.126	0.07	-0.042	0.56	-0.166	0.03
NGF	-0.137	0.34	-0.181	0.18	-0.016	0.85	0.039	0.79	0.097	0.50	0.052	0.31
NT-PROBNP	-0.027	0.74	-0.041	0.64	-0.023	0.78	0.029	0.77	-0.010	0.92	-0.034	0.70
OPG	-0.080	0.31	-0.059	0.50	0.041	0.53	0.108	0.31	0.174	0.12	0.036	0.49
Osteocalcin	0.029	0.76	-0.028	0.79	-0.020	0.75	0.077	0.43	0.172	0.10	0.072	0.27
PAI-1(Active)	0.078	0.23	0.046	0.47	-0.030	0.63	-0.035	0.70	-0.013	0.89	0.009	0.82
PAI-1(Total)	0.059	0.28	0.026	0.51	-0.029	0.58	0.061	0.28	0.053	0.26	-0.005	0.90
Pancreatic polypeptide	0.010	0.91	0.025	0.78	0.015	0.81	0.038	0.66	0.075	0.38	0.039	0.42
PYY	0.041	0.60	0.025	0.73	-0.023	0.64	0.092	0.24	0.042	0.50	-0.044	0.33
Resistin	0.019	0.71	-0.026	0.60	-0.054	0.22	-0.017	0.82	-0.026	0.73	-0.017	0.65
Serum Amyloid-A	0.052	0.61	0.092	0.41	0.034	0.74	-0.070	0.55	-0.071	0.50	0.027	0.73
Serum Amyloid-P	0.086	0.60	0.133	0.30	0.024	0.89	0.094	0.59	-0.086	0.55	-0.168	0.37
SCD40L	0.183	0.13	0.021	0.87	-0.152	0.08	0.297	0.02	0.164	0.20	-0.119	0.21
TGF $\alpha$	-0.025	0.88	-0.100	0.53	-0.022	0.82	-0.044	0.75	-0.102	0.43	-0.065	0.42
TNF $\alpha$	0.064	0.44	0.002	0.99	-0.049	0.50	-0.060	0.47	-0.070	0.44	0.055	0.35
Testosterone	-0.242	0.08	-0.390	0.01	-0.108	0.05	-0.039	0.77	0.007	0.96	0.031	0.49

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VEGF	0.049	0.66	0.026	0.81	-0.003	0.96	-0.129	0.34	-0.069	0.57	0.044	0.53
hsCRP	0.101	0.34	0.032	0.78	-0.096	0.33	-0.088	0.42	-0.086	0.38	0.032	0.69
sESelectin	0.008	0.88	-0.056	0.26	-0.062	0.14	0.060	0.20	0.042	0.35	-0.007	0.79
sFas	-0.062	0.39	-0.047	0.55	0.027	0.51	0.132	0.02	0.127	0.03	0.005	0.85
sFasL	0.002	0.99	-0.001	1.00	0.013	0.87	0.052	0.64	-0.005	0.97	-0.031	0.63
sICAM	0.033	0.46	-0.071	0.09	-0.093	0.02	0.057	0.15	0.045	0.26	-0.011	0.63
sVCAM	0.072	0.15	0.016	0.62	-0.046	0.33	0.082	0.05	0.051	0.22	-0.025	0.23

\*Linear regression models testing association of GRS with baseline log-transformed biomarker levels, adjusted by Clinical center networks and source of genetic data (ACCSET or ANYSET).

\*\*Linear regression models testing association of GRS with 12-month log-transformed biomarker levels, adjusted by blood pressure and Lipid trial assignments, Clinical center networks and source of genetic data (ACCSET or ANYSET).

§ Linear regression models testing association of GRS with change in log-transformed biomarker levels from baseline to 12-months, adjusted by blood pressure and Lipid trial assignments, Clinical center networks and source of genetic data (ACCSET or ANYSET).

‡Significant at p<0.0005 (Bonferroni adjusted).

**Supplementary Table S3. Effect of rs57922 on ΔGLP-1 levels, adjusting for different covariates**

Model	Intensive glycemc arm [N=162]		Standard glycemc arm [n=189]		rs57922 x treatment interaction
	Fold change* (95% CI)	P-value	Fold change* (95% CI)	P-value	P-value
Model 1 <sup>#</sup>	0.78 (0.68-0.89)	0.0005	0.97 (0.83-1.13)	0.68	0.049
Model 2 <sup>§</sup>	0.77 (0.67-0.89)	0.0004	0.98 (0.84-1.15)	0.82	0.035
Model 3 <sup>‡</sup>	0.80 (0.69-0.92)	0.0023	0.98 (0.84-1.15)	0.82	0.048
Model 4 <sup>¶</sup>	0.81 (0.71-0.93)	0.0029	0.97 (0.83-1.13)	0.70	0.090
Model 5 <sup>†</sup>	0.78 (0.67-0.90)	0.0008	0.98 (0.83-1.16)	0.82	0.053
Model 6 <sup>‡</sup>	0.78 (0.67-0.89)	0.0005	0.97 (0.83-1.13)	0.66	0.046
Model 7 <sup>Σ</sup>	0.78 (0.68-0.90)	0.0007	0.97 (0.84-1.13)	0.73	0.054
Model 8 <sup>Λ</sup>	0.79 (0.68-0.90)	0.0010	0.96 (0.82-1.12)	0.61	0.082

\*Fold change of GLP-1 levels obtained from generalized linear regression models for association of rs57922 risk allele (T) with change in 12-month GLP-1 levels from baseline

<sup>#</sup>Model 1 adjustments included blood pressure and lipid trials and assignments within them, clinical center networks, and source of genetic data (ACCSET or ANYSET).

<sup>§</sup>Model 2 adjustments included those for Model 1 + baseline CVD, duration of diabetes, baseline glycated hemoglobin (HbA1c) and smoking status

<sup>‡</sup>Model 3 adjustments included those for Model 2 +age, sex

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<sup>¶</sup>Model 4 adjustments included those for Model1+ baseline BMI and delta BMI (change from baseline to 12 months of follow-up)

<sup>†</sup>Model 5 adjustments included those for Model1+ baseline HbA1c and delta HbA1c (change from baseline to 12 months of follow-up)

<sup>‡</sup>Model 6 adjustments included those for Model1+ baseline fasting plasma glucose (FPG) and delta FPG (change from baseline to 12 months of follow-up)

<sup>§</sup>Model 7 adjustments included those for Model1+ baseline heart rate (HR) and delta HR (change from baseline to 12 months of follow-up)

<sup>¶</sup>Model 8 adjustments included those for Model1+ baseline eGFR and delta eGFR (change from baseline to 12 months of follow-up). Note that eGFR (glomerular filtration rate) was obtained from 4 variable MDRD equation (ml/min/1.73 m<sup>2</sup>).

**Supplementary Table S4. Age and Sex sub-group analysis for association of rs57922 with delta GLP-1 levels**

Subgroup	Intensive glyceimic arm			Standard glyceimic arm			rs57922 x treatment interaction
	N	Fold change* (95% CI)	P-value	N	Fold change* (95% CI)	P-value	P-value
Un-stratified	162	0.77 (0.67-0.89)	0.0004	189	0.98 (0.84-1.15)	0.82	0.035
Females ≥61y	37	0.94 (0.66-1.35)	0.76	51	1.04 (0.60-1.82)	0.88	0.80
Males ≥61y	54	0.61 (0.47-0.79)	0.0006	71	0.94 (0.86-1.05)	0.29	0.0009
Females <61y	27	0.78 (0.56-1.09)	0.17	33	0.73 (0.46-1.17)	0.20	0.41
Males <61y	44	0.91 (0.74-1.13)	0.42	34	0.35 (0.09-1.37)	0.28	0.41

\*Fold change of GLP-1 levels obtained from generalized linear regression models for association of rs57922 risk allele (T) with change in 12-month GLP-1 levels from baseline. Covariates included sub-trials, clinical center networks, source of genetic data, baseline HbA1c, prior CVD, diabetes duration and smoking. The 61y cut-off for categorization was the median age of subjects in the intensive arm.

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**Supplementary Table S5. BMI and delta BMI sub-group analysis for association of rs57922 genotypes with GLP-1 levels in Intensive glyceemic arm**

Subgroup	Intensive glyceemic arm			Standard glyceemic arm			rs57922 x treatment interaction
	N	Fold change* (95% CI)	P-value	N	Fold change* (95% CI)	P-value	P-value
Un-stratified	162	0.80 (0.70-0.92)	0.002	189	0.97 (0.83-1.13)	0.70	0.06
BMI<35	95	0.74 (0.61-0.89)	0.0025	135	0.93 (0.76-1.14)	0.47	0.099
BMI≥35	67	0.92 (0.75-1.13)	0.43	54	1.00 (0.79-1.27)	0.99	0.35
Delta BMI<1.77	105	0.78 (0.66-0.94)	0.009	173	0.97 (0.83-1.13)	0.20	0.05
Delta BMI≥1.77	53	0.98 (0.81-1.18)	0.80	14	0.90 (0.17-4.62)	0.28	0.69

\*Fold change in GLP-1 levels obtained from generalized linear regression models for association of rs57922 risk allele (T) with change in 12-month GLP-1 levels from baseline. Covariates included sub-trials, clinical center networks, source of genetic data, age, gender and smoking. BMI≥35 represents NHLBI defined clinical category of severely obese. Delta BMI=1.77 is the upper tertile threshold for change in BMI from baseline to 12months in the intensive arm.

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**Supplementary Table S6. Drug distribution within rs57922 genotype groups at 12 months**

Drug class N (%)	Intensive glycemc arm [N=161]				Standard glycemc arm [N=189]			
	CC (n=47)	CT (n=79)	TT (n=35)	P	CC (n=50)	CT (n=93)	TT (n=46)	P
Thiazolidinediones	42 (89)	65 (82)	26 (74)	0.20	19 (38)	41 (44)	19 (41)	0.78
Biguanides	43 (91)	68 (86)	27 (77)	0.18	43 (86)	77 (83)	35 (76)	0.43
Meglitinides	14 (30)	18 (23)	9 (26)	0.68	0 (0)	0 (0)	1 (2)	0.21
Sulfonylureas	29 (62)	45 (57)	19 (54)	0.78	30 (60)	47 (51)	26 (57)	0.53
Alpha glucosidase inhibitors	0 (0)	0 (0)	1 (3)	0.22	0 (0)	0 (0)	0 (0)	-
Any insulin	26 (55)	49 (62)	21 (60)	0.76	16 (32)	36 (39)	10 (22)	0.13

**Supplementary Table S7. Effect of rs57922 on delta GLP-1 levels with adjustments for various therapeutic drugs**

Model adjustments	Intensive glycemc arm		Standard glycemc arm		SNP x treatment
	<i>Fold change*</i> (95% CI)	<i>P</i>	<i>Fold change*</i> (95% CI)	<i>P</i>	<i>P for interaction</i>
Unadjusted by drugs <sup>#</sup>	0.78 (0.68-0.89)	0.0005	0.97 (0.83-1.13)	0.68	0.049
Thiazolidinediones	0.79 (0.69-0.91)	0.0016	0.97 (0.83-1.13)	0.67	0.067
Biguanides	0.81 (0.70-0.92)	0.0025	0.96 (0.82-1.12)	0.59	0.052
Meglitinides	0.78 (0.68-0.90)	0.0005	0.97 (0.83-1.13)	0.67	0.059
Sulfonylureas	0.78 (0.68-0.89)	0.0005	0.97 (0.83-1.13)	0.71	0.048
Any insulin	0.78 (0.68-0.89)	0.0006	0.97 (0.84-1.14)	0.74	0.048

\*Fold change in GLP-1 levels obtained from generalized linear regression models for association of rs57922 risk allele (T) with change in 12-month GLP-1 levels from baseline.

<sup>#</sup>Basic model adjustments included blood pressure and lipid trials and assignments within them, clinical center networks, and source of genetic data.

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**Supplementary Table S8. Random-effects multi-tissue meta-analysis of rs57922 eQTLs from GTEx for genes affecting GLP-1 synthesis/secretion**

Gene	Name	Location	Tissues <sup>#</sup>	Beta (SE)	P-val*	P for heterogeneity
GCG	glucagon	2q24.2	13	-0.017 (0.03)	0.5101	0.84
PCSK1	proprotein convertase subtilisin/kexin type 1	5q15	30	0.002 (0.01)	0.8511	0.37
GLP1R	glucagon like peptide 1 receptor	6p21.2	16	0.01 (0.02)	0.6590	0.81
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit-alpha	3q26.32	33	-0.003 (0.01)	0.7027	0.26
DPP4	dipeptidyl peptidase 4	2q24.2	28	0.008 (0.01)	0.4972	0.99
KCNQ1	potassium voltage-gated channel subfamily Q member1	11p15.5	31	-0.014 (0.01)	0.2161	0.46
TCF7L2	transcription factor 7 like 2	10q25.2	33	0.01 (0.01)	0.4105	0.29
SLC2A5	solute carrier family 2 member 5	1p36.23	33	-0.03 (0.01)	<b>0.0316</b>	0.32
SLC5A1	solute carrier family 5 member 1	22q12.3	14	-0.054 (0.02)	<b>0.0039</b>	0.99
SLC5A4	solute carrier family 5 member 4	22q12.3	30	0.027 (0.02)	0.1419	0.98
GRPR	gastrin releasing peptide receptor	Xp22.2	21	-0.06 (0.02)	<b>0.0009</b>	0.97
GIPR	gastric inhibitory polypeptide receptor	19q13.32	33	0.0003 (0.01)	0.98	0.45
SSTR5	somatostatin receptor 5	16p13.3	19	-0.02 (0.02)	0.23	0.34
GABRA1	gamma-aminobutyric acid type A receptor alpha1 subunit	5q34	13	0.01 (0.02)	0.38	0.40
INSR	Insulin receptor	19p13.2	33	-0.01 (0.01)	0.24	0.52
LEPR	Leptin receptor	1p31.3	33	-0.043 (0.01)	<b>0.0007</b>	0.86
FFAR4	Free fatty acid receptor 4	10q23.33	25	0.02 (0.02)	0.15	0.47
SLC27A1	Solute carrier family 27 member 1	19p13.11	33	-0.007 (0.01)	0.40	0.38
PRKCZ	Protein kinase C zeta	1p36.33	33	0.007 (0.01)	0.44	0.91
MAPK3	Mitogen-activated protein kinase 3	16p11.2	33	-0.009 (0.01)	0.36	0.75

<sup>#</sup>Number of tissues with eQTL data for rs57922 in the Genotype-Tissue-Expression (GTEx) database. Tissues queried include cardiovascular, endocrine, gut, brain and inflammatory tissues. \*Significant p-values ( $\leq 0.05$ ) in bold. 4 of 20 genes tested were significant (Binomial  $P=0.01$ ).