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van Dongen, J.

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Supplement to chapter 5*

* Based on: van Dongen J, Willemsen G., Heijmans B.T., Neuteboom J., Kluit C, Jansen R, Penninx BWJ, Slagboom PE, Geus EJ, Boomsma DI. Longitudinal weight differences, gene expression, and blood biomarkers in BMI discordant identical twins (*accepted for publication by the International Journal of Obesity*).

Supplemental Methods

1. Subjects

MZ twins were registered with the Netherlands Twin Register (NTR). The majority of twins was recruited through City Councils between 1990 and 1993 when they were adolescents or young adults. Zygosity assessment was based on DNA markers for 55% of all MZ pairs, for 91.4 % of MZ pairs included in the analysis of blood biomarker profiles and for 96.6% of MZ pairs included in the analysis of gene expression profiles. For the remaining pairs, zygosity was based on validated survey items or blood groups.

2. NTR survey studies

2.1 Quality checks BMI data

For subjects who completed multiple surveys at age 18 or older, height values were averaged to obtain one measure of adult body height if the difference in height reported by an individual across time did not exceed 2 cm. If different self-reports differed by 3 cm or more, the most deviating report was removed and the remaining values were averaged if the difference between remaining values was less than 3 cm. If the difference in height reported by an individual at different surveys was 3 or 4 cm after removal of two outlier values, remaining values were averaged to obtain one measure of adult height. Height data were considered unreliable and therefore not used if the difference in height reported by an individual at different surveys still exceeded 4 cm after removal of two outlier values. Height and weight assessed in lab-based studies were used to validate survey-based data on height and weight.

2.2 Quality checks birth weight data

Data on birth weight were collected as part of multiple NTR surveys and projects. Data reported by the twins themselves and / or by their parents were combined and consistency across family members and time was checked. When multiple data points differed, the average was taken, but only if the difference was smaller than 200 grams.

2.3 Lifestyle characteristics

Data on eating habits and leisure time exercise activities were obtained from the eighth NTR survey study (2009). Eating habits were assessed by the following questions: 1. Did you ever go on a diet to lose weight or to avoid gaining weight? 2. How scared are you to gain weight or become fat? 3. How fast do you normally eat? 4. Do you normally eat until you feel full? 5. Who of you eats most (you and your co-twin)? Exercise activities were assessed with the following questions: 1. Do you participate in leisure time exercise activities regularly? (yes/no) 2. How often do you participate in these activities (4 answer categories, ranging from “almost never” to > 10 hours per week)?

Current smoking status was assessed in all NTR surveys and as part of the NTR biobank project. To assess whether changes in smoking status may contribute to changes in BMI discordance over time, individuals were grouped into four categories based on their smoking status at two time points (the time point of first discordance and at the first next time point, ≥ 1 year later): 1. “non-smoker” (non-smoker at both time

points), 2. “started smoking” (non-smoker at first time point, smoker at the second time point), 3. “smoker” (smoker at both time points), and quit smoking (“smoker at first time point and non-smoker at second time point).

For further information about lifestyle data obtained through surveys, we refer the reader to previous papers that reported on these variables: eating ¹⁻⁴, smoking ⁵⁻⁷, leisure time exercise participation ^{8,9}.

3. NTR biobank project

3.1 Study protocol and measures

In total, 9992 subjects participated in the NTR biobank project, including monozygotic and dizygotic twins and their family members. For a detailed description of the biobank study protocol, see Willemsen *et al*¹⁰. In short, venous blood samples were drawn in the morning after an overnight fast and usually in the subjects' home, to measure blood biomarker profiles and gene expression. Additionally, information on height, weight and a range of health-related variables such as medication use and smoking status were obtained. In the current study, data on lipid-lowering medication (user/non-user) and medication for diabetes (user/non-user) are analyzed. Female twins were asked if they were pregnant or if they had entered menopause at the moment of blood draw. In the current analyses, cigarette smoking status at blood draw was assessed by two variables: current-smoking (current smoker/ non-smoker) and smoking ever (ever-smoked/never-smoked).

3.2 Blood biomarkers

Total cholesterol, high-density lipoprotein cholesterol (HDL) and triglyceride levels were measured in heparin plasma and low-density lipoprotein cholesterol (LDL) was calculated with the Friedewald Equation ¹¹. Glucose and insulin were measured in heparin plasma. TNF- α , IL-6, and sIL-6R were measured in EDTA plasma, CRP level was measured in heparin plasma, and fibrinogen level was measured in CTAD plasma. The liver enzymes Gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were determined in heparin plasma. For further details on the measurements of blood biomarker profiles, see Willemsen *et al*¹⁰. Because the distributions of insulin, triglycerides, CRP, TNF-alpha, IL-6, AST, ALT and GGT were skewed, an LN-transformation was applied to these variables to obtain a normal distribution. For insulin, TNF- α , and GGT extreme outlier values identified by inspection of the distribution of the data from discordant pairs were adjusted: For insulin, 1 value of 300.8 μ IU/ml was changed to 109.9 μ IU/ml, which corresponds to 3 times the SD above the mean of the LN-transformed distribution. For TNF-alpha, 1 value of 266.80 pg/mL was changed to 2.5 pg/mL, which corresponds to 4 times the SD above the mean of the LN-transformed distribution. For GGT, 4 values (5.06 U/L, 5.11 U/L, 5.26 U/L and 4.87 U/L), were changed to 4.85 U/L, which corresponds to 3 times the SD above the mean of the LN-transformed distribution. Following the same procedure, 1 extreme outlier value in the analysis of BMI concordant twins who became discordant after blood draw was identified and adjusted: for insulin, 1 value of 109 μ IU/ml was changed to 34.8 μ IU/ml, which corresponds to 3 times the SD above the mean of the LN-transformed distribution in this group of twins.

3.3 Gene Expression

RNA extraction¹⁰, expression profiling and expression QC procedures have been described in detail previously¹². In short, PAXgene tubes were shipped to the Rutgers University Cell and DNA Repository (RUCDR), USA. RNA was extracted using Qiagen Universal liquid handling system (PAXgene extraction kits as per the manufacturer's protocol). Total RNA was determined using spectroscopy (Trinean DropSense) to determine purity and concentration (total yield is calculated from these values) while RNA fidelity was measured by the Agilent Bioanalyzer analysis. Samples were hybridized to Affymetrix U219 array plates (GeneTitan), which contain 530,467 probes for 49,293 transcripts, each with a length of 25 bases. Array hybridization, washing, staining, and scanning were carried out in an Affymetrix GeneTitan System per the manufacturer's protocol. Probes were excluded if they did not pass standard Affymetrix QC metrics (Affymetrix expression console), if they did not map uniquely to Human Genome build 19 (hg19), or if they contained a polymorphic SNP based on snp137 (UCSC). Expression values were obtained using Robust Multi-array Average (RMA) normalization implemented in Affymetrix Power Tools (APT, v 1.12.0). The data from MZ twin pairs used in the current study are part of a larger dataset in which expression was measured and normalized jointly¹². After quality control, gene expression data were available for 634 complete MZ pairs with data on BMI and all covariates for which the expression data were corrected (e.g. blood cell counts).

4. Analyses

4.1 Correction for multiple testing of biomarkers, lifestyle and health variables

The number of dimensions in the data was determined using Matrix Spectral Decomposition (matSpD, "<http://gump.qimr.edu.au/general/daleN/matSpD/>"). MatSpD was applied to all data from all MZ twin pairs, except for gene expression data and the question about which of the twins eats most. Although this variable is informative in the within-twin pair comparison, it is not informative when computing correlations between variables across individuals, because the variable does not give insight into the actual amount a person eats (it only gives insight into the food intake relative to the co-twin). Among the total number of 32 variables used as input for MatSpD, 26 effective independent variables were identified based on the formula by Li et al¹³. Including the question about which twin eats most, we thus tested 27 independent variables, resulting in a significance threshold of 0.002 at a Type I error rate at 5%.

4.2 Gene Expression Analysis - Gene Ontology analysis

To test for enrichment of Gene Ontology (GO) terms among probe sets with stronger expression differences between discordant twins, all probe sets were ranked by P-value from the paired t-test and the resulting ranked gene list was supplied to the online software tool GOrilla (47). This tool performs GO enrichment analysis in gene lists based on rank, using information from all genes tested in discordant twins (i.e. no p-value cut-off is required to define the input list of genes). The analysis was run with default settings.

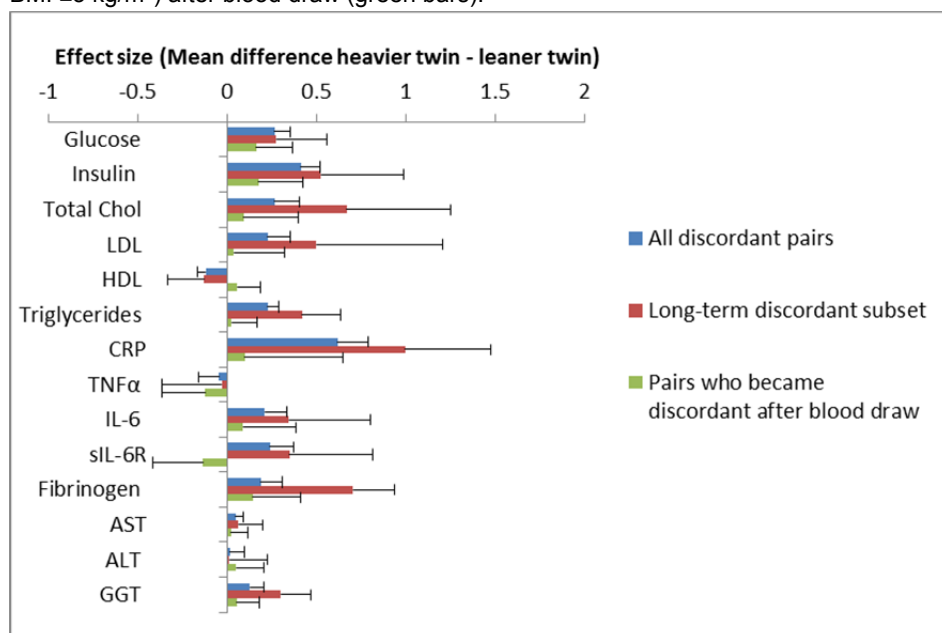
4.3 Gene Expression Analysis - Gene Set Enrichment Analysis of BMI loci from GWAS

Gene set enrichment analysis (GSEA) of loci identified in a genome-wide association analysis of BMI¹⁴ was conducted with the software package GSEA, using default

settings^{15, 16}. To obtain a set of 'candidate genes for BMI' we selected the 28 nearest genes from genome-wide significant SNPs as described by Speliotes *et al*¹⁴. Our expression dataset included 23 of these genes, targeted by 67 probe sets in total. In our final set of candidate BMI loci from GWAS, we only included probe sets that were expressed in blood (N=34 probe sets, N=18 genes, see Supplemental Table 2). Expressed probe sets were defined as probe sets of which the average expression level across all MZ twins was \geq the average expression level in females of probe sets targeting chromosome Y. According to this criterion, 30 609 probe sets in total had an average expression level above the threshold (69% of all probe sets), and 13 632 had an average below the threshold.

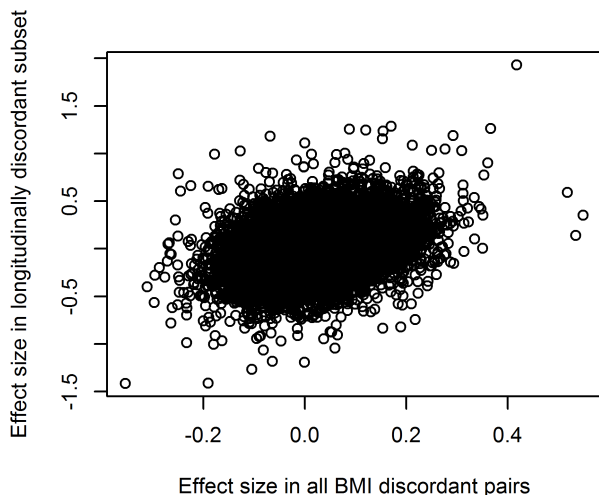
Supplemental Figures

Supplemental Figure 1: Effect sizes from the comparison of biomarkers (heavier twin - leaner twin) in all pairs who were BMI discordant at blood draw (blue bars), the longitudinally discordant subset (red bars), and MZ pairs who became discordant (Δ BMI ≥ 3 kg/m²) after blood draw (green bars).

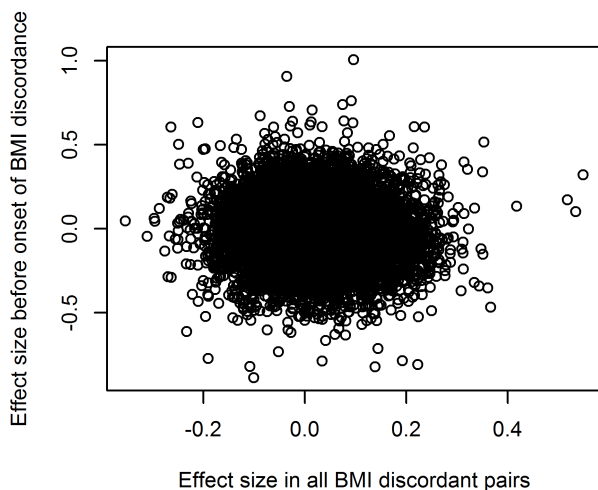


Error bars depict 95% confidence intervals.

Supplemental Figure 2: Effect sizes (heavier twin - leaner twin) from the comparison of gene expression level at each probe set in all pairs who were BMI discordant at blood draw (x-axis), and the longitudinally discordant subset (y-axis).



Supplemental Figure 3: Effect sizes (heavier twin - leaner twin) from the comparison of gene expression level at each probe set in all pairs who were BMI discordant at blood draw (x-axis), and MZ pairs who became discordant ($\Delta \text{BMI} \geq 3 \text{ kg/m}^2$) after blood draw (y-axis).



Supplemental Tables

Supplemental Table 1: Number and frequency of MZ pairs with a BMI difference ≥ 2 or ≥ 3 at 0, 1 or multiple time points

	Never	1 time point	2 time points	≥ 3 time points	Total N pairs ^A
BMI difference ≥ 2	529 (45.8%)	290 (25.1%)	154 (13.3%)	181 (15.7%)	1154
BMI difference ≥ 3	797 (69.1%)	201 (17.4%)	74 (6.4%)	82 (7.1%)	1154

^A The table includes only pairs who participated in at least three NTR projects (N total=1154 pairs).

Supplemental Table 2: Characteristics of BMI discordant MZ twin pairs followed over time

	Heavier twin at baseline	Leaner twin at baseline
	Mean (SD) or N (%)	Mean (SD) or N (%)
All pairs		
Number of pairs	305	
Age (years) baseline	33.6 (14.4), range 13-80	
BMI (kg/m ²) baseline	26.2 (3.7)	21.8 (3.2)
BMI difference (kg/m ²) baseline	4.3 (1.5), range=3.0-14.0	
Years between baseline & follow-up	3.4 (2.2), range=1-16	
BMI difference (kg/m ²) follow-up	3.1 (2.3), range: 0-12.5	
Converging pairs		
Number of pairs	169 (55.4%)	
BMI difference 2-3 at follow-up	64%	
BMI difference 1-2 at follow-up	49%	
BMI difference <1 at follow-up	56%	
Age (years) baseline	32.0 (13.7)	
BMI difference (kg/m ²) baseline	4.08 (1.4)	
BMI (kg/m ²) baseline	25.4 (3.3)	21.3 (3.2)
BMI (kg/m ²) follow-up	23.6 (3.1)	23.1 (3.0)
Weight change (kg)	-2.9 (6.8)	5.2 (6.1)
Smoking status ^A	69	71
Non-smoker at both time points	34 (49.3%)	30 (42.2%)
Started smoking	10 (14.5%)	2 (2.8%)
Smoker at both time points	22 (31.9%)	29 (40.8%)
Quit smoking	3 (4.3%)	10 (14.8%)
Pairs who are still discordant at follow-up		
Number of pairs	136 (44.6%)	
Age (years) base line	35.6 (14.9)	
BMI difference (kg/m ²) baseline	4.7 (1.6)	
BMI (kg/m ²) baseline	27.2 (3.9)	22.5 (3.2)
BMI (kg/m ²) follow-up	28.0 (4.3)	23.2 (3.6)
Weight change (kg)	2.6 (7.0)	2.2 (5.6)
Smoking status ^B	65	53
Non-smoker at both time points	29 (54.7%)	25 (38.5%)
Started smoking	5 (9.4%)	3 (4.6%)
Smoker at both time points	17 (32.1%)	28 (43.1%)
Quit smoking	2 (3.8%)	9 (13.8%)

^A Wilcoxon signed rank test in converging pairs: p-value=0.012

^B Wilcoxon signed rank test in pairs who are still discordant at follow-up: p-value=0.086

Supplemental Table 3: Gene expression results MZ pairs discordant at blood draw.

Paired t-test results for the Top 100 probe sets from the comparison in all MZ pairs who were discordant at blood draw

Probeset ID	Gene	chr	bp start	bp end	Mean difference (Heavy twin- lean twin)	P-value	q-value
X11722037_at	CRYBA2	chr2	219854911	219858135	-0.1559575	2.22E-05	0.29495
X11738909_a_at	H1FOO	chr3	129267844	129269652	-0.266928667	4.49E-05	0.29495
X11720432_s_at	TFEB	chr6	41651716	41652816	-0.22880975	4.52E-05	0.29495
X11753998_a_at	CD58	chr1	117064409	117078850	0.311937083	5.19E-05	0.29495
X11721835_s_at	TMEM14B	chr6	10756700	10757214	0.206527917	5.76E-05	0.29495
X11744544_s_at	KDELR1	chr19	48885827	48886584	-0.141909833	6.40E-05	0.29495
X11761957_x_at		chr4	419224	432421	0.3348195	6.62E-05	0.29495
X11748304_a_at	ENTPD6	chr20	25202428	25207365	-0.150988917	6.90E-05	0.29495
X11723536_a_at	SPATA8	chr15	97328226	97328845	-0.1734235	7.11E-05	0.29495
X11715818_at	ZFP36L2	chr2	43449541	43452891	-0.139368583	0.000101767	0.380147
X11744580_x_at		chr18	32885940	32890730	0.230477667	0.000119316	0.405181
X11743279_x_at	WNK1	chr12	1017641	1020618	0.22331075	0.000130267	0.405506
X11746677_x_at	REXO1	chr19	1815248	1816568	-0.167292	0.000151961	0.407011
X11762707_a_at	C14orf182	chr14	50469467	50474238	-0.149497583	0.000152542	0.407011
X11747719_a_at	RP11-173D9.3	chr14	35739607	35743497	0.1403315	0.000187525	0.435791
X11743066_s_at	PTDSS1	chr8	97345685	97349223	0.18558875	0.00019626	0.435791
X11718381_a_at	PSD4	chr2	113958735	113960814	-0.186774333	0.000226454	0.435791
X11718609_a_at	VPS72	chr1	151146867	151149540	-0.1965665	0.0002282	0.435791
X11733403_x_at	CLEC7A	chr12	10269376	10271189	0.232779667	0.000232062	0.435791
X11751906_a_at	PTPRM	chr18	8406107	8406859	0.263364417	0.000237758	0.435791
X11731446_s_at	SNCA	chr4	90645250	90647811	0.322955083	0.000251742	0.435791
X11720682_at	TIFA	chr4	113196783	113199590	0.20228125	0.000261257	0.435791
X11757341_s_at	OPTN	chr10	13178745	13180291	0.23637175	0.000268326	0.435791
X11715810_a_at	TRIP12	chr2	230631930	230633435	0.172217833	0.00028818	0.448535
X11737820_a_at	MAP3K3	chr17	61769093	61773663	-0.261552	0.000330068	0.473931
X11716095_s_at	KLF6	chr10	3818188	3821782	0.110515583	0.000330793	0.473931
X11739687_a_at	FAM107B	chr10	14560556	14563305	0.203113917	0.000350644	0.473931
X11750531_a_at	PYCARD	chr16	31212806	31214771	-0.152709417	0.000355246	0.473931
X11739095_a_at	PCSF7	chr11	61170121	61179409	-0.183803833	0.000378095	0.475697
X11739339_s_at	FAM46C	chr1	118165464	118170994	0.312222417	0.000404466	0.475697
X11754960_a_at	PRRT2	chr16	29824311	29827201	-0.174264917	0.000404628	0.475697
X11731132_s_at	JRK	chr8	143738874	143747746	0.193752917	0.000413249	0.475697
X11720466_a_at	ARL6IP1	chr16	18802991	18804692	-0.286802333	0.000435947	0.475697
X11740534_x_at	PTGES3L	chr17	41120105	41121203	-0.08969375	0.00043676	0.475697
X11726022_a_at	FAM177A1	chr14	35522406	35548230	0.21662525	0.00045696	0.475697
X11732358_x_at	ZNRF1	chr16	75127470	75144611	-0.175354	0.000472791	0.475697
X11748248_a_at	CKAP2	chr13	53049030	53050485	0.222333	0.000472939	0.475697
X11749102_a_at	SECISBP2	chr9	91972914	91974557	0.177691417	0.000492534	0.475697
X11716233_a_at	CTNBP1	chr1	9908334	9910834	-0.16573925	0.000520889	0.475697
X11759560_s_at	SLC25A37	chr8	23428848	23432976	0.138722083	0.000548822	0.475697
X11723368_a_at	ARHGEF6	chrX	135747706	135750328	0.111911167	0.000583576	0.475697
X11719076_a_at	REEP1	chr2	86441116	86444233	-0.123607667	0.000584063	0.475697
X11746767_a_at	ITGA4	chr2	182347241	182351036	0.194040833	0.000590018	0.475697
X11763763_a_at	DGKA	chr12	56333199	56334682	-0.1891795	0.000598581	0.475697
X11737437_a_at	CNTLN	chr9	17502549	17503921	-0.097775667	0.000603245	0.475697
X11723078_s_at	CXorf26	chrX	75397451	75398039	0.26485675	0.000603365	0.475697
X11761337_at	TRMT2A	chr22	20102488	20103303	-0.166182583	0.000620511	0.475697
X11725142_a_at	TGS1	chr8	56717452	56738007	0.226291833	0.000621967	0.475697
X11717189_x_at	DNAJA1	chr9	33036572	33039905	0.18519575	0.000659125	0.475697
X11729260_a_at	ZNF644	chr1	91403829	91406866	0.287202417	0.0006716	0.475697
X200010_PM_at		chr1	24018796	24020403	0.19060025	0.000679053	0.475697
X11728932_x_at	FXYP7	chr19	35642157	35645204	-0.138288833	0.000732285	0.475697
X11746235_a_at	LIN37	chr19	36243077	36244721	-0.195913333	0.000759223	0.475697
X11761810_at	FUK	chr16	70500785	70501869	-0.187282917	0.00076224	0.475697
X11760760_x_at	UCHL5	chr1	192989017	192989586	0.141950417	0.000765789	0.475697

X11731369_x_at		chr19	12460185	12462132	-0.19750175	0.000769483	0.475697
X11757971_s_at	THAP5	chr7	108202959	108205549	0.51778925	0.000776868	0.475697
X11744359_s_at	MBD3	chr19	1576677	1578537	-0.275785	0.000788131	0.475697
X11734263_at	ZNF780A	chr19	40575059	40582116	0.205208583	0.000816413	0.475697
X11743512_x_at	KDM4B	chr19	5151346	5153606	-0.186464583	0.000832775	0.475697
X11742518_at	OR7G2	chr19	9212945	9213982	-0.229504333	0.000839003	0.475697
X11746510_x_at	PSMD6	chr3	63996225	64004383	0.245186417	0.000852269	0.475697
X11750306_x_at	RP11-770J1.4	chr11	118303836	118305921	-0.065328417	0.000863184	0.475697
X11745492_a_at	CCNO	chr5	54528595	54529508	-0.112790667	0.000875228	0.475697
X11726606_at	MTF2	chr1	93602227	93604638	0.2138585	0.000888109	0.475697
X11741451_a_at	RDM1	chr17	34245070	34245447	-0.2009395	0.000891303	0.475697
X11762406_s_at	GBP2	chr1	89571815	89572735	0.194151167	0.000900771	0.475697
X11737758_x_at	CARS	chr11	3022152	3033506	0.162189167	0.000914648	0.475697
X11717992_a_at	DNAJC7	chr17	40129279	40134421	0.1758085	0.000930425	0.475697
X11732675_at	RNF180	chr5	63665442	63668696	-0.0680505	0.00093238	0.475697
X11761082_at	HINFP	chr11	119000570	119003283	-0.122547	0.000972815	0.475697
X11717432_a_at	ECHDC1	chr6	127609855	127611422	0.2918125	0.000973988	0.475697
X11743450_a_at	ELOVL6	chr4	110967002	110972918	-0.1433735	0.001002042	0.475697
X11744744_a_at	SLITRK3	chr3	164904508	164908639	-0.114370917	0.001029278	0.475697
X11756604_a_at	PCDH2	chr5	140474227	140476962	-0.095217333	0.001032168	0.475697
X11727706_a_at	BBC3	chr19	47724079	47725175	-0.154623667	0.001050753	0.475697
X11735117_at	VAMP4	chr1	171669300	171673674	0.183243	0.001054273	0.475697
X11739386_at	CDC73	chr1	193219806	193223031	0.1948555	0.001091936	0.475697
X11741283_a_at	AKAP7	chr6	131602670	131604675	0.160234167	0.001123274	0.475697
X11754982_x_at		chr22	29694723	29696515	0.111470333	0.001118688	0.475697
X11756383_a_at	FARSB	chr2	223478530	223478647	0.227243833	0.00112136	0.475697
X11760039_a_at	LRP1	chr12	57542764	57543842	-0.16667475	0.001139725	0.475697
X11721136_a_at	CMC2	chr16	81009698	81010076	0.19487475	0.001142803	0.475697
X11755873_a_at	ACSS1	chr20	24986868	24988577	0.131453083	0.001156619	0.475697
X11719998_a_at	SYNJ2BP	chr14	70838148	70883778	-0.2325685	0.001165786	0.475697
X11729846_a_at	BST1	chr4	15733363	15734410	0.2108295	0.001178086	0.475697
X11728358_a_at	FAM13B	chr5	137273649	137276037	0.15703675	0.001203324	0.475697
X11751373_a_at	PDGFC	chr4	157681606	157689142	0.1944855	0.001206933	0.475697
X11736605_a_at	XPO7	chr8	21862506	21864096	0.159236083	0.001207148	0.475697
X11739000_a_at	SLC38A2	chr12	46751972	46754992	0.174002	0.0012289	0.475697
X11719604_a_at	PTPN9	chr15	75759462	75761324	-0.182001917	0.00126991	0.475697
X11760832_at		chr6	170870879	170871321	-0.161687917	0.001276276	0.475697
X11726511_a_at	TCHP	chr12	110340832	110344445	-0.156983583	0.001305642	0.475697
X11757873_x_at	ATP5B	chr12	57031959	57033976	0.126153417	0.001325367	0.475697
X11718016_a_at	ADARB1	chr21	46641933	46646478	0.187034917	0.001328605	0.475697
X11746565_a_at	CHSY1	chr15	101715928	101719185	-0.2250135	0.001330175	0.475697
X11755199_a_at	C11orf35	chr11	554855	555930	-0.179232667	0.001344629	0.475697
X11758700_s_at		chr10	112363989	112364394	0.548986833	0.001381421	0.475697
X11748417_a_at	PROX1	chr1	214178508	214214853	-0.113066667	0.001393676	0.475697
X11759563_a_at	EPC1	chr10	32556679	32558063	0.21392525	0.001408086	0.475697

Supplemental Table 3 Continued

Results of the enrichment analysis of GO processes in the expression data from all MZ pairs who were discordant at blood draw

GO Term	Description	P-value	FDR q-value	Enrichment N	B	n	b	
GO:0043170	macromolecule metabolic process	3.84E-06	4.66E-02	1.16	16602	5774	1786	720
GO:0044260	cellular macromolecule metabolic process	5.00E-06	3.04E-02	1.17	16602	5299	1757	656
GO:0044238	primary metabolic process	5.68E-06	2.30E-02	1.13	16602	7088	1772	857
GO:0008152	metabolic process	7.50E-06	2.28E-02	1.12	16602	7813	1772	934
GO:0080090	regulation of primary metabolic process	9.69E-06	2.35E-02	1.21	16602	4536	1374	455
GO:0071704	organic substance metabolic process	1.81E-05	3.67E-02	1.12	16602	7354	1772	881
GO:2000737	negative regulation of stem cell differentiation	1.83E-05	3.17E-02	33.69	16602	9	219	4
GO:0044237	cellular metabolic process	2.30E-05	3.50E-02	1.12	16602	7139	1768	855
GO:0070365	hepatocyte differentiation	2.57E-05	3.46E-02	31	16602	9	238	4
GO:0010638	positive regulation of organelle organization	3.19E-05	3.88E-02	3.22	16602	274	376	20
GO:0019222	regulation of metabolic process	3.57E-05	3.95E-02	1.19	16602	5044	1374	495
GO:0031323	regulation of cellular metabolic process	4.36E-05	4.42E-02	1.2	16602	4549	1374	451
GO:0032480	negative regulation of type I interferon production	4.82E-05	4.50E-02	6.62	16602	34	664	9
GO:0043280	positive regulation of cysteine-type endopeptidase activity involved in apoptotic process	4.86E-05	4.21E-02	5.14	16602	104	373	12
GO:0045963	negative regulation of dopamine metabolic process	6.21E-05	5.03E-02	178.52	16602	2	93	2
GO:0045914	negative regulation of catecholamine metabolic process	6.21E-05	4.71E-02	178.52	16602	2	93	2
GO:0019538	protein metabolic process	7.79E-05	5.57E-02	1.23	16602	2829	1786	373
GO:0006974	cellular response to DNA damage stimulus	9.32E-05	6.29E-02	1.77	16602	597	941	60
GO:2001056	positive regulation of cysteine-type endopeptidase activity	9.42E-05	6.02E-02	4.81	16602	111	373	12

GO:0006793	phosphorus metabolic process	1.02E-04	6.22E-02	1.56	16602	1639	610	94
GO:0009892	negative regulation of metabolic process	1.06E-04	6.10E-02	1.31	16602	1563	1778	220
GO:0032880	regulation of protein localization	1.09E-04	6.04E-02	1.69	16602	460	1435	67
GO:0010950	positive regulation of endopeptidase activity	1.49E-04	7.85E-02	4.6	16602	116	373	12
GO:0097193	intrinsic apoptotic signaling pathway	1.51E-04	7.63E-02	2.22	16602	154	1410	29
GO:2001242	regulation of intrinsic apoptotic signaling pathway	1.53E-04	7.44E-02	3.16	16602	106	891	18
GO:0009987	cellular process	1.55E-04	7.24E-02	1.07	16602	11666	1626	1217
GO:0090200	positive regulation of release of cytochrome c from mitochondria	1.62E-04	7.28E-02	6.21	16602	24	891	8
GO:0031325	positive regulation of cellular metabolic process	1.77E-04	7.68E-02	1.28	16602	2049	1526	242
GO:0006796	phosphate-containing compound metabolic process	1.88E-04	7.86E-02	1.55	16602	1599	610	91
GO:0060255	regulation of macromolecule metabolic process	1.95E-04	7.89E-02	1.16	16602	4300	1781	537
GO:2000484	positive regulation of interleukin-8 secretion	1.99E-04	7.81E-02	188.66	16602	8	22	2
GO:0010952	positive regulation of peptidase activity	2.03E-04	7.70E-02	4.45	16602	120	373	12
GO:0009893	positive regulation of metabolic process	2.12E-04	7.80E-02	1.25	16602	2164	1780	290
GO:0044267	cellular protein metabolic process	2.30E-04	8.23E-02	1.24	16602	2353	1786	313
GO:0045321	leukocyte activation	2.35E-04	8.16E-02	1.68	16602	333	1777	60
GO:0022603	regulation of anatomical structure morphogenesis	2.69E-04	9.07E-02	1.52	16602	673	1456	90
GO:2000482	regulation of interleukin-8 secretion	3.32E-04	1.09E-01	150.93	16602	10	22	2
GO:0008219	cell death	3.37E-04	1.08E-01	1.47	16602	831	1410	104
GO:1901990	regulation of mitotic cell cycle phase transition	3.38E-04	1.05E-01	2.39	16602	221	754	24
GO:0032026	response to magnesium ion	3.43E-04	1.04E-01	159.63	16602	13	16	2
GO:0010604	positive regulation of macromolecule metabolic process	3.57E-04	1.06E-01	1.26	16602	1959	1780	264
GO:1901360	organic cyclic compound metabolic process	3.77E-04	1.09E-01	1.17	16602	4164	1625	477
GO:0016265	death	3.91E-04	1.11E-01	1.47	16602	835	1410	104
GO:0010467	gene expression	3.91E-04	1.08E-01	1.51	16602	588	1641	88
GO:0008150	biological_process	3.98E-04	1.07E-01	1.04	16602	13924	1778	1548
GO:0048522	positive regulation of cellular process	4.63E-04	1.22E-01	1.2	16602	3381	1540	376
GO:0031324	negative regulation of cellular metabolic process	5.20E-04	1.35E-01	1.3	16602	1448	1778	201
GO:0031057	negative regulation of histone modification	5.28E-04	1.34E-01	35.47	16602	26	54	3
GO:1901987	regulation of cell cycle phase transition	5.45E-04	1.35E-01	2.32	16602	228	754	24
GO:0051246	regulation of protein metabolic process	5.61E-04	1.36E-01	1.27	16602	1704	1781	232
GO:0015937	coenzyme A biosynthetic process	5.77E-04	1.37E-01	8.75	16602	11	862	5
GO:0050808	synapse organization	5.83E-04	1.36E-01	2.5	16602	107	1367	22
GO:0090199	regulation of release of cytochrome c from mitochondria	5.90E-04	1.35E-01	5.48	16602	36	673	8
GO:0006919	activation of cysteine-type endopeptidase activity involved in apoptotic process	6.09E-04	1.37E-01	5.14	16602	78	373	9
GO:0006725	cellular aromatic compound metabolic process	6.40E-04	1.41E-01	1.17	16602	3955	1625	453
GO:0070265	necrotic cell death	6.65E-04	1.44E-01	8.47	16602	11	891	5
GO:0033554	cellular response to stress	6.78E-04	1.46E-01	1.45	16602	1078	1118	105
GO:0048518	positive regulation of biological process	7.01E-04	1.47E-01	1.18	16602	3774	1540	413
GO:0001775	cell activation	7.27E-04	1.50E-01	6.24	16602	532	35	7
GO:0060216	definitive hemopoiesis	7.28E-04	1.47E-01	5.04	16602	13	1774	7
GO:0051171	regulation of nitrogen compound metabolic process	7.95E-04	1.58E-01	1.21	16602	3559	1285	332
GO:0046483	heterocycle metabolic process	8.01E-04	1.57E-01	1.16	16602	3942	1720	475
GO:0043412	macromolecule modification	8.15E-04	1.57E-01	1.24	16602	1986	1786	265
GO:0046649	lymphocyte activation	8.35E-04	1.59E-01	1.69	16602	271	1777	49
GO:0001879	detection of yeast	8.43E-04	1.58E-01	1,185.86	16602	1	14	1
GO:0032469	endoplasmic reticulum calcium ion homeostasis	8.57E-04	1.58E-01	12.69	16602	12	436	4
GO:0090161	Golgi ribbon formation	8.66E-04	1.57E-01	14.09	16602	3	1178	3
GO:0070201	regulation of establishment of protein localization	8.83E-04	1.58E-01	1.65	16602	393	1435	56
GO:0051945	negative regulation of catecholamine uptake involved in synaptic transmission	9.64E-04	1.70E-01	1,037.62	16602	1	16	1
GO:0070494	regulation of thrombin receptor signaling pathway	9.64E-04	1.67E-01	1,037.62	16602	1	16	1
GO:0070495	negative regulation of thrombin receptor signaling pathway	9.64E-04	1.65E-01	1,037.62	16602	1	16	1
GO:0051585	negative regulation of dopamine uptake involved in synaptic transmission	9.64E-04	1.63E-01	1,037.62	16602	1	16	1
GO:0051622	negative regulation of norepinephrine uptake	9.64E-04	1.60E-01	1,037.62	16602	1	16	1
GO:0051621	regulation of norepinephrine uptake	9.64E-04	1.58E-01	1,037.62	16602	1	16	1
GO:0033043	regulation of organelle organization	9.69E-04	1.57E-01	2.08	16602	636	376	30
GO:0043001	Golgi to plasma membrane protein transport	9.89E-04	1.58E-01	8.98	16602	20	462	5

Results of the enrichment analysis of GO functions in the expression data from all MZ pairs who were discordant at blood draw

GO Term	Description	P-value	FDR q-					
			value	Enrichment	N	B	n	b
GO:0005515	protein binding	1.09E-08	4.32E-05	1.15	16602	7785	1791	964
GO:0044822	poly(A) RNA binding	1.76E-06	3.49E-03	1.58	16602	1003	1309	125
GO:0005488	binding	2.39E-06	3.17E-03	1.08	16602	11600	1788	1343
GO:0097159	organic cyclic compound binding	3.62E-06	3.59E-03	1.21	16602	5318	1223	474
GO:1901363	heterocyclic compound binding	4.03E-06	3.20E-03	1.21	16602	5245	1249	477
GO:0003723	RNA binding	8.06E-05	5.34E-02	1.35	16602	1342	1730	189
GO:0003676	nucleic acid binding	1.71E-04	9.71E-02	1.2	16602	3481	1625	409
GO:0036094	small molecule binding	2.04E-04	1.01E-01	1.29	16602	2417	1223	230
	guanosine-5'-triphosphate, 3'-diphosphate							
GO:0008894	diphosphatase activity	4.22E-04	1.86E-01	2,371.71	16602	1	7	1
GO:1901265	nucleoside phosphate binding	5.21E-04	2.07E-01	1.29	16602	2161	1223	206
GO:0000166	nucleotide binding	5.21E-04	1.88E-01	1.29	16602	2161	1223	206
GO:0004844	uracil DNA N-glycosylase activity	5.50E-04	1.82E-01	80.59	16602	4	103	2
GO:0097506	deaminated base DNA N-glycosylase activity	5.50E-04	1.68E-01	80.59	16602	4	103	2
GO:0001874	(1->3)-beta-D-glucan receptor activity	8.43E-04	2.39E-01	1,185.86	16602	1	14	1
GO:0001873	polysaccharide receptor activity	8.43E-04	2.23E-01	1,185.86	16602	1	14	1

Supplemental Table 3 Continued
Results of the enrichment analysis of GO components in the expression data from all MZ pairs who were discordant at blood draw

GO Term	Description	P-value	FDR q-value	Enrichment	N	B	n	b
GO:0043231	intracellular membrane-bounded organelle	2.26E-08	3.16E-05	1.21	16602	6234	1285	585
GO:0044428	nuclear part	5.57E-08	3.91E-05	1.36	16602	2142	1719	302
GO:0043229	intracellular organelle	1.10E-07	5.16E-05	1.18	16602	7227	1240	638
GO:0044424	intracellular part	2.50E-07	8.77E-05	1.08	16602	11466	1756	1314
GO:0043227	membrane-bounded organelle	3.96E-07	1.11E-04	1.17	16602	7202	1265	644
GO:0044446	intracellular organelle part	9.50E-07	2.22E-04	1.17	16602	5875	1769	730
GO:0032991	macromolecular complex	1.36E-06	2.73E-04	1.22	16602	3985	1781	520
GO:0043226	organelle	2.36E-06	4.14E-04	1.15	16602	8058	1265	704
GO:0031968	organelle outer membrane	3.13E-06	4.88E-04	3.6	16602	129	714	20
GO:0019867	outer membrane	5.42E-06	7.60E-04	3.47	16602	134	714	20
GO:0043234	protein complex	1.29E-05	1.64E-03	1.22	16602	3506	1781	457
GO:0005794	Golgi apparatus	1.34E-05	1.57E-03	1.71	16602	522	1471	79
GO:0044422	organelle part	1.52E-05	1.64E-03	1.15	16602	6053	1769	739
GO:0005634	nucleus	5.15E-05	5.16E-03	1.22	16602	3981	1285	377
GO:0072559	NLRP3 inflammasome complex	1.64E-04	1.54E-02	13.79	16602	5	963	4
GO:0005768	endosome	1.69E-04	1.48E-02	1.74	16602	370	1471	57
GO:0005654	nucleoplasm	2.22E-04	1.83E-02	1.39	16602	1028	1656	143
GO:0031010	ISWI-type complex	2.25E-04	1.75E-02	6.93	16602	9	1596	6
GO:0031090	organelle membrane	3.64E-04	2.69E-02	1.29	16602	2263	1214	214
GO:0005737	cytoplasm	5.28E-04	3.71E-02	1.19	16602	3139	1730	390
GO:0005741	mitochondrial outer membrane	5.49E-04	3.67E-02	3.29	16602	106	714	15
GO:0005681	spliceosomal complex	5.94E-04	3.79E-02	2.03	16602	136	1746	29
GO:0098588	bounding membrane of organelle	6.70E-04	4.08E-02	1.45	16602	1795	663	104
GO:0044444	cytoplasmic part	7.41E-04	4.33E-02	1.11	16602	6524	1769	773
GO:1902494	catalytic complex	9.76E-04	5.48E-02	1.42	16602	713	1776	108

N - is the total number of genes

B - is the total number of genes associated with a specific GO term

n - is the number of genes in the top of the input list

b - is the number of genes in the intersection

Enrichment = (b/n) / (B/N)

Supplemental Table 3 Continued BMI candidate genes from GWAS

Probeset ID	Gene	chr	bp start	bp end	Mean difference (Heavy twin- lean twin)	P-value
X11757158_x_at	RPL27A	chr11	8705553	8706439	-0.265600833	0.01726931
X11722222_at	TMEM160	chr19	47549168	47551882	-0.139438083	0.042584018
X11728331_a_at	KCTD15	chr19	34302696	34306666	-0.072732167	0.112544529
X11722804_x_at	PTBP2	chr1	97278829	97280349	0.10804825	0.122102125
X11755163_a_at	FANCL	chr2	58386378	58386935	0.120043833	0.14734394
X11763807_at	MAP2K5	chr15	67951109	67951694	-0.059615333	0.154978677
X11757157_at	RPL27A	chr11	8705553	8706439	-0.152119917	0.167965257
X11749270_a_at	GPRC5B	chr16	19868616	19871866	0.058514417	0.178945818
X11723064_a_at	TMEM18	chr2	667335	670975	-0.037379833	0.192874871
X11748421_a_at	TMEM18	chr2	667335	669675	0.062703667	0.215433744
X11758115_s_at	PTBP2	chr1	97278829	97280349	0.059483167	0.283516582
X11735168_a_at	QPCTL	chr19	46205056	46207247	0.048152833	0.289610822
X11757335_s_at	MTIF3	chr13	28009776	28014586	0.057331	0.332608659
X11735738_x_at	SH2B1	chr16	28884768	28885526	-0.036996167	0.371866712
X11719312_a_at	MAP2K5	chr15	68061940	68099461	-0.053008667	0.384309664
X11758687_s_at	TMEM18	chr2	667335	669675	0.057649333	0.388020616
X11723450_a_at	FTO	chr16	54145674	54155853	0.05670125	0.444320049
X11728061_a_at	ZNF608	chr5	123982372	123984826	-0.054238417	0.447142328
X11721075_a_at	MTCH2	chr11	47638868	47650907	0.03643175	0.480440294
X11748888_a_at	FTO	chr16	53967897	54155853	-0.034729667	0.600806646
X11723451_x_at	FTO	chr16	54145674	54155853	0.03448675	0.601559716
X11722380_at	NUDT3	chr6	34255997	34256708	0.033521417	0.603998358
X11748612_a_at	ETV5	chr3	185764097	185775033	-0.019385083	0.642919699
X11724249_a_at	SLC39A8	chr4	103188647	103189236	0.026031333	0.652173182
X11762571_a_at	GNPDA2	chr4	44703885	44705159	0.0190655	0.652820119
X11721866_a_at	GNPDA2	chr4	44703885	44705159	0.020161917	0.655448171
X11719175_a_at	GPRC5B	chr16	19868616	19873662	0.00949025	0.745942093
X11749835_x_at	SH2B1	chr16	28883855	28885526	-0.014989	0.761435581
X11724252_s_at	SLC39A8	chr4	103182823	103184350	-0.017443917	0.775788688
X11719176_a_at	GPRC5B	chr16	19868616	19871866	0.016042667	0.789953565

X11721076_at	MTCH2	chr11	47638867	47640471	0.00940325	0.884434048
X11721867_a_at	GNPDA2	chr4	44703885	44705159	-0.006933333	0.91246732
X11740764_at	SLC39A8	chr4	103172198	103174587	-0.005699167	0.91704398
X11720353_s_at	ETV5	chr3	185764097	185766649	-0.002964667	0.943630725

Supplemental Table 3 Continued

SIZ	NOM p-	FDR q-	FWER p-	RANK AT		
E	ES	NES	val	val	val	MAX
LEADING EDGE						
18	0.288449	0.7147	0.923076	0.923076	0.912	7970 tags=44%, list=44%,

Supplemental Table 4: Gene expression results MZ pairs discordant in longitudinally discordant MZ pairs.

Paired t-test results for the Top 100 probe sets from the comparison in longitudinally discordant MZ pairs

Probeset ID	Gene	chr	bp start	bp end	Mean difference	P-value	q-value
					(Heavy twin- lean twin)		
X11727799_at	CHRM1	chr11	62676151	62678650	-0.330721111	5.17E-06	0.22888
X11721227_at	LEMD3	chr12	65639080	65642107	-0.395771111	5.12E-05	0.999482
X11737263_at	HRK	chr12	117293949	117319246	-0.769828889	0.000107	0.999482
X11736257_at	PRKCE	chr2	46411874	46415129	-0.482706667	0.000113	0.999482
X11757638_s_at	CD93	chr20	23059986	23064611	-0.246394444	0.000134	0.999482
X11716725_a_at	ADCY6	chr12	49159975	49162499	-0.33289	0.000161	0.999482
X11746884_a_at	RAD52	chr12	1021243	1022618	0.418235556	0.000235	0.999482
X11739853_a_at	SNX16	chr8	82711816	82736175	0.406994444	0.000253	0.999482
X11732927_x_at	KLRC1	chr12	10598627	10599261	1.247322222	0.000255	0.999482
X11760342_a_at	PPP3CB	chr10	75203538	75204580	0.620455556	0.000267	0.999482
X11733165_s_at	YIPF5	chr5	143537723	143540123	0.563431111	0.000283	0.999482
X11761097_at	ARFGAP2	chr11	47194649	47195033	-0.509937778	0.000316	0.999482
X11747816_a_at	GDAP1	chr8	75276220	75279111	0.395358889	0.000377	0.999482
X11727636_at	RERGL	chr12	18233803	18234407	-0.170217778	0.000381	0.999482
X11763763_a_at	DGKA	chr12	56333199	56334682	-0.720315556	0.000468	0.999482
X11750678_a_at	ALK	chr2	29415640	29416788	-0.283086667	0.000481	0.999482
X11744971_at	PSORS1C3	chr6	31141512	31145676	0.26571	0.000545	0.999482
X11734853_x_at	SCEL	chr13	78208514	78219398	-0.321234444	0.000554	0.999482
X11742211_x_at	APP	chr21	27252861	27264180	-0.25373	0.000558	0.999482
X11748086_a_at	PIK3CG	chr7	106545554	106547590	-0.46727	0.000569	0.999482
X11747177_x_at	AQP1	chr7	30963065	30965131	-0.339784444	0.000611	0.999482
X11754790_a_at	FAM193A	chr4	2701407	2702271	-0.467374444	0.000633	0.999482
X11729436_a_at	LY6H	chr8	144239331	144239902	-0.358746667	0.000643	0.999482
X11718198_at	LHFP	chr13	39917029	39918191	-0.324992222	0.000701	0.999482
X11756615_x_at	SHMT2	chr12	57627786	57628718	0.569896667	0.000825	0.999482
X11738272_a_at	PSMG4	chr6	3259128	3259430	-0.677882222	0.000854	0.999482
X11717611_a_at	MAST2	chr1	46500210	46501896	-0.328534444	0.000863	0.999482
X11733161_a_at	TNFAIP8	chr5	118728511	118730294	0.592585556	0.000866	0.999482
X11748265_a_at	LDLRAD3	chr11	36250710	36253686	-0.472254444	0.000899	0.999482
X11733199_a_at	CCDC14	chr3	123632300	123634565	-0.322354444	0.000912	0.999482
X11764211_at	RP11-71J4.2	chr12	68738444	68743739	0.303654444	0.000928	0.999482
X11742468_at	RASSF10	chr11	13031083	13032647	-0.430362222	0.000932	0.999482
X11739911_at	PCBD2	chr5	134246025	134296967	-0.414174444	0.000989	0.999482
X11725151_at	MYBP3	chr11	47352957	47354253	-0.348562222	0.001034	0.999482
X11724825_a_at	DOLK	chr9	131707809	131709898	0.622142222	0.001047	0.999482
X11731978_s_at	PCSK7	chr11	117075053	117077072	-0.195322222	0.001049	0.999482
X11731694_s_at	HIST1H2AE	chr6	26217165	26217711	0.302743333	0.001095	0.999482
X11746570_s_at	FRYL	chr4	48499378	48502237	0.339261111	0.001222	0.999482
X11729288_at	MSL3	chrX	11783586	11786096	-0.402761111	0.001311	0.999482
X11756760_a_at	GCDH	chr19	13010282	13010953	0.385726667	0.001334	0.999482
X11731795_at	EPHX4	chr1	92518067	92529093	0.267196667	0.001334	0.999482
X11752620_s_at	YPEL5	chr2	30381485	30383399	0.291173333	0.001364	0.999482
X11761010_a_at	CKMT1B	chr15	43889574	43890525	-0.305822222	0.001379	0.999482
X11736644_a_at	G6PC2	chr2	169764078	169766505	0.099615556	0.001387	0.999482
X11732685_a_at	POGZ	chr1	151375200	151378940	0.57982	0.001405	0.999482
X11742589_at	OR4L1	chr14	20528204	20529142	0.30026	0.001464	0.999482
X11741689_s_at	SUMF2	chr7	56147221	56148363	1.003967778	0.001498	0.999482
X11737235_x_at	USP6	chr17	5076100	5078329	-0.56039	0.001501	0.999482
X11718800_at	PTPRU	chr1	29652111	29653325	-0.405303333	0.001595	0.999482
X11763585_s_at	TMPO	chr12	98941351	98944157	0.521868889	0.001596	0.999482
X11740546_a_at	ADAM22	chr7	87825786	87832204	-0.191864444	0.001633	0.999482
X11731577_a_at	SLC22A1	chr6	160560685	160579750	-0.488166667	0.001701	0.999482

X11738116_a_at	GABRQ	chrX	151821004	151825999	-0.177167778	0.001705	0.999482
X11745014_at	WT1-AS	chr11	32459391	32462950	0.615003333	0.001745	0.999482
X11733302_at	ZNF790	chr19	37308330	37311016	-0.45587	0.001745	0.999482
X11741702_a_at	ABHD11	chr7	73152000	73152472	-0.341222222	0.001746	0.999482
X11754466_a_at	SH3BP4	chr2	235962236	235964358	-0.422815556	0.001761	0.999482
X11733195_a_at	FMNL3	chr12	50031724	50039686	-0.568922222	0.001828	0.999482
X11724990_s_at	CLTCL1	chr22	19166986	19167482	0.361827778	0.001868	0.999482
X11744490_x_at	C20orf24	chr20	35236118	35240960	0.539621111	0.001914	0.999482
X11752864_a_at	FER	chr5	108207066	108295048	-0.503152222	0.001972	0.999482
X11741281_a_at	AKAP7	chr6	131571299	131571756	-0.551327778	0.002016	0.999482
X11732809_a_at	PROK2	chr3	71820807	71821979	0.256727778	0.002052	0.999482
X11736562_at	ZNF518A	chr10	97915954	97923517	0.577573333	0.002063	0.999482
X11727800_a_at	POP4	chr19	30104732	30108144	0.336887778	0.002087	0.999482
X11730156_a_at	WVOX	chr16	78143675	78149051	-0.670443333	0.002088	0.999482
X11749252_a_at	STOM	chr9	124101355	124103686	0.41952	0.002109	0.999482
X11760847_at	KCNMB1	chr5	169809656	169810854	-0.288943333	0.002133	0.999482
X11761341_at	SLC9A1	chr1	27431942	27432578	-0.353345556	0.002145	0.999482
X11734260_a_at	TRIML1	chr4	189067976	189068897	-0.334801111	0.002149	0.999482
X11732738_a_at	CECR2	chr22	18032535	18033845	-0.538021111	0.002157	0.999482
X11735074_at	C15orf37	chr15	80215113	80217194	0.856636667	0.002197	0.999482
X11738946_at	MRAP	chr21	33686862	33687095	0.529556667	0.002201	0.999482
X11748052_x_at		chr11	125449989	125454575	-0.487018889	0.002213	0.999482
X11758819_x_at	RRP7A	chr22	42905974	42909001	-0.789261111	0.002215	0.999482
X11733411_at	TCF15	chr20	584441	591042	-0.384284444	0.002219	0.999482
X11746084_a_at	PCMT1	chr6	150131752	150132556	0.560476667	0.002228	0.999482
X11740650_a_at	SSH1	chr12	109176466	109183020	0.476375556	0.002286	0.999482
X11741495_a_at	KCNQ3	chr8	133139193	133142243	-0.244285556	0.002292	0.999482
X11731222_a_at	SHOX2	chr3	157813743	157816109	-0.186572222	0.002302	0.999482
X11722261_at	EDEM1	chr3	5255004	5261642	-0.493644444	0.002454	0.999482
X11717832_a_at	MIIP	chr1	12089280	12092102	-0.414705556	0.002458	0.999482
X11746675_a_at	ZNF232	chr17	5012221	5013163	-0.322361111	0.002498	0.999482
X11746844_a_at	TMEM143	chr19	48835613	48836690	-0.58645	0.002502	0.999482
X11727289_a_at	LIM2	chr19	51883164	51885821	-0.399387778	0.002517	0.999482
X11749189_s_at	HOXB3	chr17	46626232	46628543	0.36586	0.002517	0.999482
X11735404_a_at	ANKS1B	chr12	99145133	99166957	-0.264331111	0.002575	0.999482
X11752970_a_at	RAD52	chr12	1023058	1023698	0.504576667	0.002583	0.999482
X11717118_a_at	P4HA2	chr5	131527531	131530951	-0.452391111	0.00259	0.999482
X11760670_x_at	FMO3	chr1	171068946	171069876	0.223623333	0.002654	0.999482
X11724307_x_at	ORAOV1	chr11	69480331	69482355	-0.710774444	0.002668	0.999482
X11734860_a_at	WDR37	chr10	1175153	1178237	-0.46481	0.002671	0.999482
X11741548_a_at	MBNL1	chr3	152163071	152163328	0.249118889	0.002681	0.999482
X11735461_at	SPRR2B	chr1	153042704	153043334	0.239678889	0.002704	0.999482
X11748173_a_at	RIMS1	chr6	73108657	73112845	-0.252658889	0.002719	0.999482
X11740281_at	TSEN2	chr3	12571261	12573158	0.352466667	0.002734	0.999482
X11740495_x_at	SLC6A12	chr12	301644	305427	0.417687778	0.00275	0.999482
X11715678_s_at	NAP1L4	chr11	2965667	2966876	0.388807778	0.00276	0.999482
X11743251_s_at	MMP2	chr16	55539251	55540603	0.243546667	0.002763	0.999482
X11749532_a_at	RASGRF1	chr15	79282531	79291167	-0.414716667	0.002777	0.999482

Results of the enrichment analysis of GO processes in the expression data from longitudinally discordant pairs

GO Term	Description	P-value	FDR q-value	Enrichment	N	B	n	b
GO:0007169	transmembrane receptor protein tyrosine kinase signaling pathway	5.38E-05	6.53E-01	1.67	16602	528	1410	75
GO:0016192	vesicle-mediated transport	1.03E-04	6.24E-01	8.25	16602	741	19	7
GO:0001775	cell activation	1.57E-04	6.37E-01	9.85	16602	532	19	6
GO:0007167	enzyme linked receptor protein signaling pathway	1.65E-04	5.00E-01	1.53	16602	706	1442	94
GO:0042116	macrophage activation	1.76E-04	4.27E-01	255.42	16602	26	5	2
GO:0044093	positive regulation of molecular function	2.32E-04	4.70E-01	1.5	16602	1165	970	102
GO:2001031	positive regulation of cellular glucuronidation	2.41E-04	4.18E-01	4,150.50	16602	1	4	1
GO:0050878	regulation of body fluid levels	2.46E-04	3.73E-01	9.06	16602	550	20	6
GO:0065007	biological regulation	2.89E-04	3.90E-01	1.09	16602	8689	1786	1019
GO:0030168	platelet activation	3.30E-04	4.01E-01	17.56	16602	199	19	4
GO:0045760	positive regulation of action potential	3.41E-04	3.77E-01	13.73	16602	7	691	4
GO:0050789	regulation of biological process	3.43E-04	3.48E-01	1.09	16602	8229	1786	969
GO:0006810	transport	3.66E-04	3.42E-01	3.44	16602	2895	20	12
GO:0051234	establishment of localization	4.56E-04	3.96E-01	3.36	16602	2964	20	12
GO:0007207	phospholipase C-activating G-protein coupled acetylcholine receptor signaling pathway	5.27E-04	4.27E-01	5,534.00	16602	3	1	1
GO:0021546	rhombomere development	5.93E-04	4.50E-01	24.97	16602	7	285	3
GO:0038031	non-canonical Wnt signaling pathway via JNK cascade	6.78E-04	4.85E-01	20.37	16602	5	489	3
GO:0009887	organ morphogenesis	6.83E-04	4.61E-01	3.25	16602	387	185	14
GO:0019220	regulation of phosphate metabolic process	7.62E-04	4.87E-01	1.41	16602	1513	927	119
GO:0065008	regulation of biological quality	8.32E-04	5.05E-01	1.84	16602	2343	158	41
GO:2001029	regulation of cellular glucuronidation	8.33E-04	4.82E-01	2,075.25	16602	2	4	1
GO:0035668	TRAM-dependent toll-like receptor signaling pathway	8.33E-04	4.60E-01	2,075.25	16602	2	4	1
GO:0035669	TRAM-dependent toll-like receptor 4 signaling pathway	8.33E-04	4.40E-01	2,075.25	16602	2	4	1

GO:0061178	regulation of insulin secretion involved in cellular response to glucose stimulus	8.76E-04	4.43E-01	114.5	16602	29	10	2
GO:0002274	myeloid leukocyte activation	9.05E-04	4.40E-01	33.61	16602	78	19	3
GO:0050679	positive regulation of epithelial cell proliferation	9.06E-04	4.23E-01	3.02	16602	135	570	14
GO:0050794	regulation of cellular process	9.08E-04	4.09E-01	1.09	16602	7793	1786	917
GO:0051642	centrosome localization	9.16E-04	3.97E-01	5.59	16602	10	1783	6
GO:0006897	endocytosis	9.31E-04	3.90E-01	7.09	16602	270	52	6
GO:0006468	protein phosphorylation	9.80E-04	3.97E-01	1.51	16602	483	1779	78

Results of the enrichment analysis of GO functions in the expression data from longitudinally discordant pairs

GO Term	Description	P-value	FDR q-value	Enrichment	N	B	n	b
GO:0005488	binding	7.25E-05	2.88E-01	1.06	16602	11600	1786	1329
GO:0008047	enzyme activator activity	1.51E-04	3.01E-01	1.89	16602	391	1058	47
GO:0004714	transmembrane receptor protein tyrosine kinase activity	3.61E-04	4.78E-01	2.94	16602	64	1502	17
GO:0016709	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, NAD(P)H as one donor, and incorporation of one atom of oxygen	7.16E-04	7.11E-01	6.3	16602	35	527	7
GO:0005326	neurotransmitter transporter activity	7.73E-04	6.15E-01	15.2	16602	24	182	4

Results of the enrichment analysis of GO components in the expression data from longitudinally discordant pairs

GO Term	Description	P-value	FDR q-value	Enrichment	N	B	n	b
GO:0016020	membrane	6.63E-05	9.30E-02	2.45	16602	5357	24	19
GO:0044459	plasma membrane part	3.60E-04	2.53E-01	1.3	16602	2050	1296	208

N - is the total number of genes

B - is the total number of genes associated with a specific GO term

n - is the number of genes in the top of the input list

b - is the number of genes in the intersection

Enrichment = (b/n) / (B/N)

Supplemental Table 4 continued: BMI candidate genes from GWAS

Probeset ID	Gene	chr	bp start	bp end	Mean difference	P-value
X11763807_at	MAP2K5	chr15	67951109	67951694	0.261961111	0.00874709
X11721075_a_a	MTCH2	chr11	47638868	47650907	-0.413622222	0.01915122
X11748612_a_a	ETV5	chr3	185764097	185775033	0.270972222	0.06993190
X11740764_at	SLC39A8	chr4	103172198	103174587	-0.325171111	0.10781581
X11748888_a_a	FTO	chr16	53967897	54155853	-0.21378	0.12423122
X11719312_a_a	MAP2K5	chr15	68061940	68099461	0.348952222	0.12493022
X11721866_a_a	GNPDA2	chr4	44703885	44705159	-0.234468889	0.19605749
X11758687_s_a	TMEM18	chr2	667335	669675	-0.164804444	0.25353003
X11723451_x_a	FTO	chr16	54145674	54155853	0.316087778	0.26542667
X11720353_s_a	ETV5	chr3	185764097	185766649	0.111271111	0.2677416
X11728331_a_a	KCTD15	chr19	34302696	34306666	-0.113144444	0.28830922
X11762571_a_a	GNPDA2	chr4	44703885	44705159	0.180142222	0.36566345
X11719176_a_a	GPRC5B	chr16	19868616	19871866	-0.198771111	0.37758752
X11721076_at	MTCH2	chr11	47638867	47640471	-0.141058889	0.39127769
X11719175_a_a	GPRC5B	chr16	19868616	19873662	0.116055556	0.41869169
X11722380_at	NUDT3	chr6	34255997	34256708	0.147534444	0.46638071
X11722804_x_a	PTBP2	chr1	97278829	97280349	0.155097778	0.46840526
X11735168_a_a	QPCTL	chr19	46205056	46207247	-0.124088889	0.48173707
X11749835_x_a	SH2B1	chr16	28883855	28885526	0.100666667	0.53555615
X11749270_a_a	GPRC5B	chr16	19868616	19871866	0.179831111	0.55105368
X11735738_x_a	SH2B1	chr16	28884768	28885526	0.064416667	0.64409108
X11721867_a_a	GNPDA2	chr4	44703885	44705159	-0.095638889	0.66097926
X11728061_a_a	ZNF608	chr5	123982372	123984826	-0.079452222	0.66260341
X11758115_s_a	PTBP2	chr1	97278829	97280349	0.059338889	0.68194526
X11757335_s_a	MTIF3	chr13	28009776	28014586	0.060194444	0.72914422
X11722222_at	TMEM16	chr19	47549168	47551882	0.077915556	0.74948506
X11723450_a_a	FTO	chr16	54145674	54155853	0.045583333	0.79499697
X11748421_a_a	TMEM18	chr2	667335	669675	0.044701111	0.79669509
X11755163_a_a	FANCL	chr2	58386378	58386935	-0.03592	0.80997778
X11724249_a_a	SLC39A8	chr4	103188647	103189236	-0.059984444	0.82537923
X11757157_at	RPL27A	chr11	8705553	8706439	-0.07958	0.82813435
X11757158_x_a	RPL27A	chr11	8705553	8706439	-0.053602222	0.88054561
X11724252_s_a	SLC39A8	chr4	103182823	103184350	-0.005823333	0.97251022
X11723064_a_a	TMEM18	chr2	667335	670975	-0.004955556	0.97453698

Enrichment analysis output GSEA for BMI GWAS gene set

SIZ	NOM p-val	FDR q-val	FWER p-val	RANK AT	LEADING EDGE
E	ES	NES	val	MAX	
18	0.288449	0.71753	0.909274	0.902	7970 tags=44%, list=44%,

Supplemental Table 5 Gene expression results MZ pairs who became discordant after blood draw
Paired t-test results for the Top 100 probe sets from the comparison in MZ pairs who became discordant after blood draw

Probeset ID	Gene	chr	bp start	bp end	Mean difference (Heavy twin- lean twin)	P-value	q-value
X11743518_s_at	NNT	chr5	43704357	43707507	-0.365688571	1.31E-05	0.573441
X11737062_a_at	MTMR3	chr22	30421619	30426855	0.32376381	5.98E-05	0.810097
X11725284_a_at	ZFP90	chr16	68595964	68601039	-0.288890476	7.61E-05	0.810097
X11722188_at	MTDH	chr8	98736828	98740998	-0.593707619	0.000100749	0.810097
X11753045_a_at	MBNL2	chr13	98043576	98046374	-0.292324286	0.000108778	0.810097
X11753133_x_at	MCM8	chr20	5935748	5975852	-0.487959048	0.000110915	0.810097
X11741698_a_at	LCN12	chr9	139847918	139849949	0.372813333	0.000199421	0.946831
X11730425_at	ZNF628	chr19	55992568	55995854	0.390548095	0.00020386	0.946831
X11734708_at	C5orf43	chr5	60453536	60456026	-0.384932857	0.000235318	0.946831
X11723606_a_at	AGF1	chr2	228419152	228421384	-0.520450476	0.000269666	0.946831
X11752039_a_at	PHC3	chr3	169813009	169815172	-0.391388571	0.000273923	0.946831
X11721110_s_at	NAP1L3	chrX	92925929	92928567	-0.178418571	0.000288322	0.946831
X11748088_a_at	AKAP1	chr17	55191820	55198710	0.360475238	0.000334695	0.946831
X11734685_at	PABPC3	chr13	25670006	25673392	-0.208024762	0.000346304	0.946831
X11735822_at	AC093063.1	chr19	40174127	40176361	0.295154286	0.000354759	0.946831
X11750892_a_at	SLC5A7	chr2	108626688	108630450	-0.159283333	0.000367085	0.946831
X11748102_x_at	RUNX1T1	chr8	92967203	92983388	0.241191905	0.000408501	0.946831
X11740942_at		chr18	76756891	76757631	-0.182959048	0.000445227	0.946831
X11726105_s_at	PPP2R3A	chr3	135863885	135866733	-0.451051905	0.000449082	0.946831
X11742470_a_at	SLC35F4	chr14	58030640	58033282	-0.185888095	0.000534403	0.946831
X11754230_at	DBIL5P	chr17	655900	658576	0.205343333	0.000538816	0.946831
X11722929_a_at	CNKSR3	chr6	154726433	154727786	-0.138506667	0.000560886	0.946831
X11752244_a_at	KIRREL3	chr11	126300837	126301421	0.249024762	0.00062776	0.946831
X11721822_a_at	FSD1	chr19	4322983	4323843	0.363334762	0.000633987	0.946831
X11759002_at	CACNA1E	chr1	181767428	181777219	0.213613333	0.000645416	0.946831
X11719977_a_at	MMP15	chr16	58078911	58080805	-0.162205238	0.000703666	0.946831
X11758282_s_at	TUBA1C	chr12	49666036	49667114	0.242599048	0.000808715	0.946831
X11762207_at	PCOLCE-AS1	chr7	100193491	100194274	0.44369	0.000818373	0.946831
X11728618_a_at	SLC1A7	chr1	53552855	53554651	0.296800476	0.000830727	0.946831
X11725050_a_at	FAIM2	chr12	50260679	50284505	0.341319048	0.000836513	0.946831
X11732704_a_at	FGFRL1	chr4	1018693	1020685	0.483508571	0.000868256	0.946831
X11719570_at	RCHY1	chr4	76404247	76407876	-0.329786667	0.000870498	0.946831
X11723676_at	CASQ1	chr1	160171035	160171676	-0.17496	0.000914138	0.946831
X11753130_at	TM4SF1	chr3	149086809	149089654	-0.227473333	0.000936619	0.946831
X11736930_at	G6PC	chr17	41062932	41065386	0.274805238	0.000958321	0.946831
X11720580_a_at	TCF12	chr15	57578355	57582051	-0.237150952	0.000964217	0.946831
X11741102_a_at	PTN22	chr1	114375569	114381029	-0.504869524	0.000976091	0.946831
X11718075_at	IL4R	chr16	27373573	27376099	-0.349058095	0.001004522	0.946831
X11740977_a_at	ZNF574	chr19	42582739	42585717	0.423873333	0.00106909	0.946831
X11729671_s_at	FAM200B	chr4	15687859	15690724	-0.400123333	0.00108091	0.946831
X11715169_at	PLEKHG2	chr19	39914373	39919054	0.271612381	0.001086907	0.946831
X11762044_a_at		chr19	50476300	50476379	0.726696667	0.001104771	0.946831
X11738424_at	BMP10	chr2	69092613	69093703	0.328448095	0.001110323	0.946831
X11715806_a_at	SEPW1	chr19	48284365	48284645	-0.633579048	0.001126817	0.946831
X11718950_s_at	MPP5	chr14	67799497	67802536	-0.277761429	0.001147089	0.946831
X11718157_s_at	PTX3	chr3	157160155	157161417	0.26869	0.001151166	0.946831
X11728707_a_at	EMP2	chr16	10622279	10626949	0.222689524	0.001163692	0.946831
X11743328_a_at	RBBP6	chr16	24580066	24581820	0.47306381	0.001167839	0.946831
X11763461_x_at	PLCB3	chr11	64034825	64035395	0.322246667	0.001172763	0.946831
X11717730_s_at	SQLE	chr8	126033995	126034525	-0.208751429	0.001177493	0.946831
X11748418_a_at	RSPO1	chr1	38076951	38078593	0.324177143	0.001209425	0.946831
X11727339_a_at	ZBTB2	chr6	151685252	151688027	-0.436278095	0.001232832	0.946831
X11725511_a_at	SLC38A4	chr12	47158546	47168956	0.259348095	0.001235417	0.946831
X11748634_a_at	ZCCHC24	chr10	81142081	81146214	0.463185714	0.001237709	0.946831
X11731296_a_at	SPATA6L	chr9	4598326	4618110	0.30629619	0.001269753	0.946831
X11763571_at		chr1	53580248	53581904	0.353449524	0.001269863	0.946831
X11721596_s_at	CDYL	chr6	4954132	4955785	0.907460476	0.001272092	0.946831
X11744274_at	NDC80	chr18	2608699	2616634	-0.292049524	0.001292978	0.946831
X11752195_s_at	TAX1BP1	chr7	27868247	27868880	-0.262581429	0.001294817	0.946831
X11718638_a_at	ELP6	chr3	47537130	47537687	0.445229524	0.001296358	0.946831
X11744911_a_at	RIC3	chr11	8160601	8161740	0.298277143	0.00135359	0.972425
X11719535_a_at	AP3M2	chr8	42026479	42028701	0.33133	0.001394001	0.972612
X11721611_a_at	IP011	chr5	61847050	61887499	-0.557774762	0.001445969	0.972612
X11734983_a_at	GPRASP1	chrX	101908508	101914008	-0.303210476	0.001466821	0.972612
X11719601_a_at	MOXD1	chr6	132617194	132619094	0.25399619	0.001527923	0.972612

X11729134_s_at	STK24	chr13	99102455	99105463	0.281950952	0.001584065	0.972612
X11718713_a_at	SFSWAP	chr12	132249001	132262875	0.174039048	0.001613215	0.972612
X11742631_at		chr11	48366900	48367505	0.299267619	0.001634535	0.972612
X11719608_a_at	BCAR3	chr1	94027347	94027976	0.267894762	0.00164268	0.972612
X11732165_x_at	LMF1	chr16	903634	904706	0.481082857	0.001683827	0.972612
X11757625_s_at	CD200	chr3	112080390	112081659	-0.212637619	0.001700372	0.972612
X11722492_x_at	SEZ6L2	chr16	29882480	29883049	-0.318754762	0.001707191	0.972612
X11756341_a_at	RBM23	chr14	23369854	23370942	0.27126381	0.001755072	0.972612
X11734511_at	ASCL4	chr12	108168162	108170421	0.231417143	0.001759277	0.972612
X11741941_at	GML	chr8	143921832	143928262	0.449686667	0.001765515	0.972612
X11743531_at	AF238380.3	chrX	49644470	49647166	0.45235381	0.001800042	0.972612
X11734136_at	MTBP	chr8	121530943	121535875	-0.229165238	0.001803633	0.972612
X11735470_a_at	LGALS14	chr19	40197237	40200087	0.187409048	0.001813547	0.972612
X11753393_a_at	CA6	chr1	9017196	9031040	-0.315138095	0.001915303	0.972612
X11720046_x_at	DNAJC10	chr2	183641848	183644334	-0.292651429	0.001925568	0.972612
X11736458_x_at	CKNK6	chr19	38817820	38819660	0.382955714	0.001957909	0.972612
X11731374_a_at	IL22RA2	chr6	137464968	137466910	0.211147143	0.001987976	0.972612
X11737532_a_at	FMO5	chr1	146672734	146673086	-0.234817143	0.002169705	0.972612
X11725137_x_at	SYNGR1	chr22	39770321	39774386	0.367552857	0.002179337	0.972612
X11723902_at	PLEKHG1	chr6	151160969	151164799	-0.264667143	0.002186768	0.972612
X11752327_a_at	ZNF238	chr1	244217090	244220778	-0.392979048	0.002228575	0.972612
X11756913_s_at	NOD1	chr7	30464143	30465326	0.275504762	0.002252491	0.972612
X11743721_at	LGALS1	chr22	38071615	38074661	-0.405049048	0.002260195	0.972612
X11724938_at	DLL1	chr6	170591294	170591967	0.30033	0.00227028	0.972612
X11729725_at	ZBTB6	chr9	125670335	125674360	-0.314026667	0.002303202	0.972612
X11727058_at	MIRPS36	chr5	68525035	68525956	-0.272352381	0.002320279	0.972612
X11716456_at	RHOBTB3	chr5	95128763	95132071	0.324785714	0.002337871	0.972612
X11758157_s_at	COQ10B	chr2	198338481	198340032	-0.255466667	0.002351496	0.972612
X11747465_a_at	NDST1	chr5	149931315	149937773	-0.405833333	0.002356536	0.972612
X11756032_a_at	CBR3	chr21	37518374	37518864	0.333822381	0.002361204	0.972612
X11720273_s_at	SFT2D3	chr2	128458597	128461385	0.340614286	0.002362251	0.972612
X11739636_s_at	CDK12	chr17	37686857	37690797	-0.38296	0.002447918	0.972612
X11746040_at	ZFHX2	chr14	23990069	23999645	0.284611429	0.002448079	0.972612
X11758715_s_at	DEFB126	chr20	126056	126392	0.273578571	0.002484351	0.972612
X11721849_x_at	REEP2	chr5	137781372	137782658	0.356548571	0.002498579	0.972612

Supplemental Table 5 Continued

Results of the enrichment analysis of GO processes in the expression data from MZ pairs who became discordant after blood draw

GO Term	Description	P-value	FDR q-value	Enrichment	N	B	n	b
GO:0044802	single-organism membrane organization	6.46E-05	7.85E-01	2.09	16602	302	1024	39
GO:0061024	membrane organization	1.38E-04	8.39E-01	1.8	16602	462	1078	54
GO:0030534	adult behavior	1.50E-04	6.07E-01	6.31	16602	134	157	8
	regulation of skeletal muscle contraction by regulation of release of sequestered calcium ion	2.51E-04	7.62E-01	86.92	16602	2	191	2
GO:0014809	negative regulation of caveolin-mediated endocytosis	2.55E-04	6.19E-01	85.58	16602	2	194	2
GO:0008150	biological_process	2.61E-04	5.29E-01	1.05	16602	13924	1079	951
GO:0035265	organ growth	3.17E-04	5.49E-01	7.88	16602	15	843	6
GO:0021680	cerebellar Purkinje cell layer development	4.14E-04	6.28E-01	33.74	16602	12	123	3
GO:0022612	gland morphogenesis	4.40E-04	5.94E-01	7.36	16602	15	902	6
GO:0007006	mitochondrial membrane organization	4.45E-04	5.41E-01	3.76	16602	47	1126	12
GO:0006883	cellular sodium ion homeostasis	5.00E-04	5.52E-01	10.19	16602	5	1304	4
GO:0033554	cellular response to stress	7.36E-04	7.46E-01	1.34	16602	1078	1731	151
GO:0051205	protein insertion into membrane	7.86E-04	7.35E-01	8.65	16602	13	738	5
GO:0006974	cellular response to DNA damage stimulus	8.57E-04	7.44E-01	1.47	16602	597	1726	91
GO:0061053	somite development	8.62E-04	6.98E-01	85.8	16602	9	43	2
GO:0071451	cellular response to superoxide	8.63E-04	6.55E-01	5.82	16602	11	1557	6
GO:0019430	removal of superoxide radicals	8.63E-04	6.17E-01	5.82	16602	11	1557	6
GO:0051716	cellular response to stimulus	8.78E-04	5.93E-01	1.16	16602	4545	1473	468
GO:0051336	regulation of hydrolase activity	8.81E-04	5.64E-01	1.47	16602	901	1180	94
GO:1902667	regulation of axon guidance	8.92E-04	5.42E-01	6.49	16602	16	959	6

Results of the enrichment analysis of GO functions in the expression data from MZ pairs who became discordant after blood draw

GO Term	Description	P-value	FDR q-value	Enrichment	N	B	n	b
GO:0008750	NAD(P)+ transhydrogenase (AB-specific) activity	6.02E-05	2.39E-01	16,602.00	16602	1	1	1
GO:0003957	NAD(P)+ transhydrogenase (B-specific) activity	6.02E-05	1.20E-01	16,602.00	16602	1	1	1
GO:0008746	NAD(P)+ transhydrogenase activity	2.39E-04	3.16E-01	8,301.00	16602	2	1	1
	oxidoreductase activity, acting on NAD(P)H, NAD(P) as acceptor	2.39E-04	2.37E-01	8,301.00	16602	2	1	1
GO:0004714	transmembrane receptor protein tyrosine kinase activity	2.99E-04	2.38E-01	4.07	16602	64	764	12
GO:0008331	high voltage-gated calcium channel activity	3.72E-04	2.46E-01	15.3	16602	10	434	4
GO:0016936	galactoside binding	4.73E-04	2.69E-01	89.26	16602	4	93	2
GO:0035662	Toll-like receptor 4 binding	6.75E-04	3.35E-01	15.69	16602	3	1058	3
GO:0045499	chemorepellent activity	6.96E-04	3.07E-01	20.16	16602	5	494	3
GO:0005307	choline:sodium symporter activity	9.04E-04	3.59E-01	1,106.80	16602	1	15	1

Supplemental Table 5 Continued

Results of the enrichment analysis of GO components in the expression data from MZ pairs who became discordant after blood draw

GO Term	Description	P-value	FDR q-value	Enrichment	N	B	n	b	
GO:0016020	membrane	5.87E-04	8.23E-01		1.15	16602	5357	1473	545
GO:0005634	nucleus	5.90E-04	4.14E-01		1.18	16602	3981	1466	415

N - is the total number of genes

B - is the total number of genes associated with a specific GO term

n - is the number of genes in the top of the input list

b - is the number of genes in the intersection

Enrichment = (b/n) / (B/N)

Supplemental Table 5 Continued, BMI candidate genes from GWAS

Probeset ID	Gene	chr	bp start	bp end	Mean difference (Heavy twin-lean twin)	P-value
X11758687_s_at	TMEM18	chr2	667335	669675	-0.224002381	0.083281052
X11722804_x_at	PTBP2	chr1	97278829	97280349	-0.264306667	0.103622433
X11757335_s_at	MTIF3	chr13	28009776	28014586	0.328060476	0.11241314
X11748421_a_at	TMEM18	chr2	667335	669675	-0.212365238	0.1512073
X11719312_a_at	MAP2K5	chr15	68061940	68099461	0.164670476	0.163720407
X11735738_x_at	SH2B1	chr16	28884768	28885526	0.139932857	0.216469668
X11724249_a_at	SLC39A8	chr4	103188647	103189236	0.146988571	0.220316839
X11721075_a_at	MTCH2	chr11	47638868	47650907	0.136092857	0.22039422
X11757158_x_at	RPL27A	chr11	8705553	8706439	0.181799048	0.235287258
X11721866_a_at	GNPDA2	chr4	44703885	44705159	0.118775238	0.237641028
X11757157_at	RPL27A	chr11	8705553	8706439	0.184607619	0.321757416
X11723451_x_at	FTO	chr16	54145674	54155853	0.19219	0.32607976
X11722222_at	TMEM160	chr19	47549168	47551882	0.128854762	0.327178263
X11721076_at	MTCH2	chr11	47638867	47640471	-0.083596667	0.377271287
X11723450_a_at	FTO	chr16	54145674	54155853	0.184607619	0.321757416
X11755163_a_at	FANCL	chr2	58386378	58386935	-0.16898381	0.417659357
X11723064_a_at	TMEM18	chr2	667335	670975	-0.041884762	0.447702709
X11719176_a_at	GPRC5B	chr16	19868616	19871866	0.10887	0.504990939
X11762571_a_at	GNPDA2	chr4	44703885	44705159	-0.048939524	0.565483882
X11719175_a_at	GPRC5B	chr16	19868616	19873662	0.048178571	0.576411552
X11749270_a_at	GPRC5B	chr16	19868616	19871866	0.068614286	0.583801443
X11724252_s_at	SLC39A8	chr4	103182823	103184350	-0.053428571	0.605300353
X11749835_x_at	SH2B1	chr16	28883855	28885526	-0.043771905	0.644212625
X11735168_a_at	QPCTL	chr19	46205056	46207247	0.042580952	0.649132758
X11728061_a_at	ZNF608	chr5	123982372	123984826	-0.048458571	0.698498727
X11758115_s_at	PTBP2	chr1	97278829	97280349	-0.049395714	0.707704728
X11728331_a_at	KCTD15	chr19	34302696	34306666	0.027834286	0.748845008
X11740764_at	SLC39A8	chr4	103172198	103174587	0.020517143	0.818440028
X11722380_at	NUDT3	chr6	34255997	34256708	0.032593333	0.839427629
X11748612_a_at	ETV5	chr3	185764097	185775033	-0.015240952	0.862888922
X11721867_a_at	GNPDA2	chr4	44703885	44705159	0.021470476	0.894685166
X11720353_s_at	ETV5	chr3	185764097	185766649	-0.009119524	0.927578069
X11763807_at	MAP2K5	chr15	67951109	67951694	0.007815238	0.941270573
X11748888_a_at	FTO	chr16	53967897	54155853	0.006940952	0.969651971

Enrichment analysis output GSEA for BMI GWAS gene set

SIZE	ES	NES	NOM p-val	FDR q-val	FWER	RANK AT	LEADING EDGE
18	0.23349632	0.580054	0.9848024	0.9848024	0.972	12650	tags=67%, list=69%,

Supplemental Reference List

1. Hsieh, S.D., Muto, T., Murase, T., Tsuji, H., & Arase, Y. Eating until feeling full and rapid eating both increase metabolic risk factors in Japanese men and women. *Public Health Nutr.* **14**, 1266-1269 (2011).
2. Maruyama, K. *et al.* The joint impact on being overweight of self reported behaviours of eating quickly and eating until full: cross sectional survey. *BMJ* **337**, a2002 (2008).

3. Ochiai,H. *et al.* Eating behavior and childhood overweight among population-based elementary schoolchildren in Japan. *Int. J. Environ. Res. Public Health* **9**, 1398-1410 (2012).
4. Ochiai,H. *et al.* The impact of eating quickly on anthropometric variables among schoolgirls: a prospective cohort study in Japan. *Eur. J. Public Health* **24**, 691-695 (2014).
5. Connor,G.S., Schofield-Hurwitz,S., Hardt,J., Levasseur,G., & Tremblay,M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. *Nicotine. Tob. Res.* **11**, 12-24 (2009).
6. Kentala,J., Utriainen,P., Pahkala,K., & Mattila,K. Verification of adolescent self-reported smoking. *Addict. Behav.* **29**, 405-411 (2004).
7. Taylor,A.E. *et al.* Investigating the possible causal association of smoking with depression and anxiety using Mendelian randomisation meta-analysis: the CARTA consortium. *BMJ Open.* **4**, e006141 (2014).
8. de Geus,E.J., Bartels,M., Kaprio,J., Lightfoot,J.T., & Thomis,M. Genetics of regular exercise and sedentary behaviors. *Twin. Res. Hum. Genet.* **17**, 262-271 (2014).
9. de Moor,M.H.M. & de Geus,E.J.C. Genetic influences on exercise behavior. in *Lifestyle Medicine* (ed. Rippe,J.M.) 1367-1378 (Taylor & Francis, Boca Raton, FL, USA, 2013).
10. Willemsen,G. *et al.* The Netherlands Twin Register biobank: a resource for genetic epidemiological studies. *Twin Res Hum Genet* **13**, 231-245 (2010).
11. Friedewald,W.T., Levy,R.I., & Fredrickson,D.S. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin. Chem.* **18**, 499-502 (1972).
12. Jansen,R. *et al.* Sex differences in the human peripheral blood transcriptome. *BMC. Genomics* **15**, 33 (2014).
13. Li,J. & Ji,L. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. *Heredity (Edinb.)* **95**, 221-227 (2005).
14. Speliotes,E.K. *et al.* Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat. Genet.* **42**, 937-948 (2010).
15. Mootha,V.K. *et al.* PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nat. Genet.* **34**, 267-273 (2003).
16. Subramanian,A. *et al.* Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc. Natl. Acad. Sci. U. S. A* **102**, 15545-15550 (2005).

