Supplementary Information

Supplementary method

1. Genome-wide association studies (GWAS) data of OP

The osteoporosis genome-wide association studies (GWAS) data set was obtained from the large-scale GWAS meta-analysis of osteoporosis from Genetic Factors for Osteoporosis Consortium (GEFOS, http://www.gefos.org/).[1] The bone mineral density (BMD) of the femoral neck, lumbar spine, and forearm were assessed via Lunar, Hologic or Norland radiograph BMD measurements following standard procedure. BMD was adjusted for age, age-squared, gender, and weight. Whole-genome sequencing, whole-exome sequencing, and SNP array testing were performed for genotyping using commercial platforms, such as Illumina HiSeq 2000 (Illumina, Inc., San Diego, California), Illumina HumanOmni1 Quad v1-0B array (Illumina, Inc., San Diego, California), or Kompetitive Allele Specific PCR (KASP) genotyping assays (LGC, Teddington, United Kingdom). Imputation analysis was conducted by IMPUTE2 software against the combined UK10K/1000 Genomes reference panel.[2-4] Meta-analysis of cohort-level common SNP association statistics was undertaken using fixed-effects meta-analysis in genome-wide association meta-analysis (GWAMA) software.[5] A total of 32 735 patients with genotype data were used for the GWAS of the neck of femur BMD, 28 498 for the lumbar spine, and 8143 for the forearm. A detailed description of the cohort information is in the paper by Zheng et al.[1]

2. Genome-wide expression quantitative trait loci (eQTLs) dataset

We used the recently published genome-wide eQTLs annotation map established by Westra et al.[6] Briefly, this eQTLs dataset was derived from a meta-analysis of 5311 samples. Gene expression profiling of blood samples was performed by Illumina whole-genome Expression BeadChips (HT12v3, HT12v4 or H8v2 arrays). SNP genotyping was evaluated by multiple chips, such as Illumina HumanHap300, HumanHap370, or the 610-Quad platforms (all Illumina, Inc., San Diego, California). Genotypes were imputed against HapMap or 1000 Genome reference panels using IMPUTE or MACH software.[2-4] eQTLs association tests were performed using Spearman's rank correlation, weighted for the square root of the sample size. We used a total of 923 021 cis-eQTLs for 14 329 gene expression probes, identified at a false discovery rate (FDR) < 0.05. A detailed description of the study subjects and experiment design can be found in the published study by Westra et al.[6] The data were pre-processed by SMR software,[7] as described in the following section.

3. Genome-wide methylation quantitative trait loci (meQTLs) dataset

A genome-wide meQTLs annotation map was obtained from the latest meQTLs study of 697 Swedish individuals by McClay et al.[8] Genotyping was conducted using Affymetrix SNP Arrays 5.0 or 6.0(Affymetrix, California, US), or Illumina OmniExpress array (Illumina, Inc., San Diego,CA). After phasing genotypes with MACH 1.0, a 1000 Genome reference panel (phase I, version 3) was employed for imputation.[2,4] Genome-wide DNA methylation was evaluated using methyl-CpG binding domain (MBD) protein-based enrichment and sequencing (MBD-seq) (SOLiD; Life Technologies, Thermo Fisher Scientific, Waltham, Massachusetts). Matrix eQTL was used for testing for association between genotype and methylation measurements. The final dataset comprised 683 152 unique methylation sites with local meQTLs, identified at FDR < 0.01.

4. Summary data-based Mendelian randomisation (SMR) analysis

SMR employed the concept of Mendelian randomisation (MR) to evaluate the effect of gene expression on traits.[7] The original MR analysis uses a genetic variant (z) as an instrumental variable to estimate and test for the causative effect of an exposure variable (x) on an outcome (y). Considering the exposure variable (x) to be the expression level of a gene, using a two-step least squares (2SLS) estimation, the effect of gene expression x on trait y can be expressed by $\hat{b}_{xy} = \frac{\hat{b}_{zy}}{\hat{b}_{zx}}$, where $\hat{b}_{zy}$ and $\hat{b}_{zx}$ are the least squares estimates of y and x on z, respectively. The sampling variance of the 2SLS estimate of $\hat{b}_{xy}$ is $\frac{\mathrm{var}(y)\left(1-R^2_{xy}\right)}{n\mathrm{var}(x)R^2_{xy}}$. Therefore, chi-squared testing statistics can be built to test the significance of $\hat{b}_{xy}$ based on $\hat{b}_{xy}$ and its variance $T_{MR} = \frac{\hat{b}^2_{xy}}{\mathrm{var}(\hat{b}_{xy})}$. Compared with directly estimating $\hat{b}_{xy}$, this two-step approach provides a more accurate estimation for effect size of x on y, free of confounding from non-genetic factors.

However, such MR analysis requires genotype, gene expression, and phenotype available in the same sample, as well as the availability of individual-level data. In comparison, SMR used expression quantitative trait loci (eQTL) SNP effect data from published eQTL studies to estimate the effect of SNP on gene expression, $\hat{b}_{zx}$. SNP effect data from existing trait GWAS summary were used to estimate SNP effect on trait, $\hat{b}_{zy}$. This yielded an adjusted statistic $T_{SMR} = \frac{\hat{b}^2_{xy}}{\mathrm{var}(\hat{b}_{xy})} \approx \frac{z^2_{zy}\, z^2_{zx}}{z^2_{zy} + z^2_{zx}}$ where z_{zy} and z_{zx} are the z statistics from a given published GWAS and eQTL study.

Table i. Expression quantitative trait loci (eQTLs)-based gene set enrichment analysis results.

Gene set name	p-value*		
	Forearm	Femoral neck	Lumbar spine
ABE_INNER_EAR	4.1E-02	1.8E-02	-
AGUIRRE_PANCREATIC_CANCER_COPY_NUMBER_UP	4.1E-02	-	3.0E-02
AMINO_SUGAR_METABOLIC_PROCESS	2.4E-02	-	4.7E-02
AMIT_SERUM_RESPONSE_240_MCF10A	3.0E-02	-	6.0E-03
ASTON_MAJOR_DEPRESSIVE_DISORDER_UP	1.3E-02	-	9.0E-03
ATGTCAC,MIR-489	1.1E-02	-	1.1E-02
BIOCARTA_P38MAPK_PATHWAY	3.9E-02	2.1E-02	-
BROWNE_HCMV_INFECTION_24HR_DN	-	2.9E-02	6.5E-03
CARBOXYLIC_ACID_TRANSPORT	1.7E-02	4.8E-02	-
CASPASE_ACTIVATION	-	4.2E-02	5.0E-02
CHIANG_LIVER_CANCER_SUBCLASS_UNANNOTATED_UP	4.0E-02	-	2.6E-02
chr11p11	4.9E-02	-	2.5E-03
chr11p15	4.6E-02	1.1E-02	-
chr11q13	3.9E-02	-	1.1E-02
chr14q31	2.1E-02	3.5E-02	-
chr3p25	-	1.1E-02	2.5E-03
CONDENSED_CHROMOSOME	3.3E-02	-	2.7E-02
CTCTATG,MIR-368	-	4.7E-02	3.2E-02
CYTOSKELETON_DEPENDENT_INTRACELLULAR_TRANSPORT	4.6E-02	-	2.6E-02
DARWICHE_PAPILLOMA_RISK_HIGH_UP	1.0E-03	4.0E-02	3.8E-02
DER_IFN_BETA_RESPONSE_UP	2.9E-02	-	3.7E-02
EHLERS_ANEUPLOIDY_UP	6.0E-03	-	2.9E-02
ESC_J1_UP_EARLY.V1_UP	-	4.5E-02	4.3E-02
GAUSSMANN_MLL_AF4_FUSION_TARGETS_A_DN	4.5E-02	-	4.0E-03
GAVIN_FOXP3_TARGETS_CLUSTER_P7	-	1.0E-02	1.2E-02
GCM_BMPR2	7.0E-03	-	3.6E-02
GCM_VAV1	-	2.4E-02	1.8E-02
GNATENKO_PLATELET_SIGNATURE	4.6E-02	-	1.0E-02
GNF2_CD48	-	1.1E-02	1.0E-02
GNF2_STAT6	2.0E-03	2.7E-02	-
GSE10240_IL17_VS_IL17_AND_IL22_STIM_PRIMARY_BRONCHIAL_EPITHELIAL_CELLS_UP	1.3E-02	-	2.1E-02
GSE12198_NK_VS_NK_ACT_EXPANSION_SYSTEM_DERIVED_NK_CELL_DN	3.7E-02	4.2E-02	-
GSE13173_UNTREATED_VS_IL12_TREATED_ACT_CD8_TCELL_DN	-	2.1E-02	7.0E-03
GSE14026_TH1_VS_TH17_DN	9.0E-03	2.2E-02	-
GSE14769_UNSTIM_VS_60MIN_LPS_BMDM_UP	8.0E-03	2.0E-02	2.1E-02
GSE14908_ATOPIC_VS_NONATOPIC_PATIENT_RESTING_CD4_TCELL_UP	-	7.5E-03	2.9E-02
GSE15324_NAIVE_VS_ACTIVATED_ELF4_KO_CD8_TCELL_UP	2.3E-02	4.5E-02	-
GSE17186_MEMORY_VS_NAIVE_BCELL_UP	2.7E-02	1.4E-02	-
GSE17721_CTRL_VS_PAM3CSK4_12H_BMDM_UP	-	4.7E-02	3.4E-02
GSE17721_LPS_VS_POLYIC_1H_BMDM_UP	-	3.4E-02	1.3E-02
GSE17721_LPS_VS_POLYIC_4H_BMDM_UP	1.5E-02	-	3.0E-02
GSE17721_PAM3CSK4_VS_CPG_12H_BMDM_UP	3.8E-02	2.8E-02	5.0E-04
GSE17721_PAM3CSK4_VS_CPG_16H_BMDM_UP	2.3E-02	-	2.1E-02
GSE17721_POLYIC_VS_CPG_1H_BMDM_DN	3.1E-02	-	1.5E-02
GSE17721_POLYIC_VS_PAM3CSK4_8H_BMDM_DN	4.0E-02	4.1E-02	-
GSE17974_CTRL_VS_ACT_IL4_AND_ANTI_IL12_1H_CD4_TCELL_UP	-	2.3E-02	2.7E-02
GSE19888_CTRL_VS_T_CELL_MEMBRANES_ACT_MAST_CELL_UP	8.5E-03	-	1.7E-02
GSE20152_HTNFA_OVERXPRESS_ANKLE_VS_CTRL_SPHK1_KO_ANKLE_UP	3.0E-03	-	4.5E-02
GSE21033_CTRL_VS_POLYIC_STIM_DC_1H_DN	6.0E-03	2.1E-02	-
GSE21380_TFH_VS_GERMINAL_CENTER_TFH_CD4_TCELL_DN	2.4E-02	-	2.3E-02
GSE22589_HEALTHY_VS_SIV_INFECTED_DC_UP	-	2.0E-03	4.3E-02
GSE22611_NOD2_VS_MUTANT_NOD2_TRANSDUCED_HEK293T_CELL_UP	3.0E-02	-	3.1E-02
GSE22886_UNSTIM_VS_IL15_STIM_NKCELL_UP	-	2.1E-02	2.1E-02
GSE24574_BCL6_HIGH_TFH_VS_TFH_CD4_TCELL_UP	4.2E-02	-	2.2E-02
GSE24634_TREG_VS_TCONV_POST_DAY3_IL4_CONVERSION_UP	4.5E-02	4.5E-02	-
GSE2585_THYMIC_DC_VS_THYMIC_MACROPHAGE_UP	3.4E-02	-	4.4E-02
GSE2770_IL4_ACT_VS_ACT_CD4_TCELL_6H_UP	2.3E-02	2.0E-03	-
GSE2770_UNTREATED_VS_TGFB_AND_IL12_TREATED_ACT_CD4_TCELL_6H_UP	-	1.4E-02	7.5E-03
GSE27786_LIN_NEG_VS_ERYTHROBLAST_DN	-	2.5E-03	2.6E-02
GSE29949_MICROGLIA_VS_DC_BRAIN_DN	3.3E-02	4.2E-02	-
GSE31082_DP_VS_CD4_SP_THYMOCYTE_DN	4.3E-02	-	6.5E-03
GSE31082_DP_VS_CD8_SP_THYMOCYTE_DN	3.2E-02	-	4.9E-02
GSE32034_LY6C_HIGH_VS_LOW_ROSIGLIZATONE_TREATED_MONOCYTE_UP	4.0E-02	2.5E-02	-
GSE32164_RESTING_DIFFERENTIATED_VS_CMYC_INHIBITED_MACROPHAGE_UP	1.3E-02	-	3.6E-02
GSE33292_DN3_THYMOCYTE_VS_TCF1_KO_TCELL_LYMPHOMA_UP	-	1.0E-03	4.0E-02
GSE33424_CD161_HIGH_VS_INT_CD8_TCELL_UP	3.0E-02	-	8.5E-03

(Continued)

Table i. (Continued)

Gene set name	p-value*		
	Forearm	**Femoral neck**	**Lumbar spine**
GSE34217_MIR17_92_OVEREXPRESS_VS_WT_ACT_CD8_TCELL_UP	2.3E-02	-	3.7E-02
GSE360_CTRL_VS_L_MAJOR_DC_DN	-	3.7E-02	1.1E-02
GSE369_PRE_VS_POST_IL6_INJECTION_SOCS3_KO_LIVER_UP	1.8E-02	-	3.5E-02
GSE37301_COMMON_LYMPHOID_PROGENITOR_VS_CD4_TCELL_UP	-	3.8E-02	4.9E-02
GSE37301_LYMPHOID_PRIMED_MPP_VS_COMMON_LYMPHOID_PROGENITOR_DN	2.0E-03	5.0E-03	-
GSE37301_MULTIPOTENT_PROGENITOR_VS_GRAN_MONO_PROGENITOR_UP	3.5E-03	5.0E-04	-
GSE37563_WT_VS_CTLA4_KO_CD4_TCELL_D4_POST_IMMUNIZATION_UP	1.0E-02	-	1.5E-02
GSE39556_CD8A_DC_VS_NK_CELL_MOUSE_3H_POST_POLYIC_INJ_UP	4.8E-02	1.3E-02	-
GSE39556_UNTREATED_VS_3H_POLYIC_INJ_MOUSE_CD8A_DC_DN	2.3E-02	2.7E-02	-
GSE3982_DC_VS_NEUTROPHIL_DN	2.4E-02	-	1.1E-02
GSE3982_EOSINOPHIL_VS_BASOPHIL_UP	1.2E-02	3.0E-03	-
GSE3982_EOSINOPHIL_VS_NKCELL_DN	3.5E-02	-	3.3E-02
GSE3982_MAC_VS_CENT_MEMORY_CD4_TCELL_DN	4.0E-03	-	2.8E-02
GSE3982_MAST_CELL_VS_DC_DN	2.6E-02	1.5E-02	-
GSE41867_NAIVE_VS_DAY30_LCMV_ARMSTRONG_MEMORY_CD8_TCELL_UP	4.7E-02	-	4.8E-02
GSE42021_CD24LO_TREG_VS_CD24LO_TCONV_THYMUS_UP	3.4E-02	-	9.0E-03
GSE43700_UNTREATED_VS_IL10_TREATED_PBMC_UP	1.1E-02	-	1.3E-02
GSE43863_DAY6_EFF_VS_DAY150_MEM_TH1_CD4_TCELL_UP	2.6E-02	-	1.5E-02
GSE43863_TH1_VS_TFH_MEMORY_CD4_TCELL_UP	1.0E-02	-	2.4E-02
GSE43955_1H_VS_60H_ACT_CD4_TCELL_UP	-	3.8E-02	3.3E-02
GSE43955_TGFB_IL6_VS_TGFB_IL6_IL23_TH17_ACT_CD4_TCELL_52H_DN	-	2.5E-02	1.9E-02
GSE43956_WT_VS_SGK1_KO_TH17_DIFFERENTIATED_CD4_TCELL_DN	1.2E-02	-	4.9E-02
GSE45365_HEALTHY_VS_MCMV_INFECTION_BCELL_IFNAR_KO_UP	4.4E-02	2.1E-02	-
GSE45365_WT_VS_IFNAR_KO_CD11B_DC_MCMV_INFECTION_UP	2.3E-02	1.2E-02	-
GSE46606_IRF4_KO_VS_WT_UNSTIM_BCELL_DN	2.7E-02	-	9.5E-03
GSE4984_GALECTIN1_VS_LPS_STIM_DC_UP	-	1.6E-02	1.2E-02
GSE5589_IL6_KO_VS_IL10_KO_LPS_AND_IL10_STIM_MACROPHAGE_45MIN_UP	4.3E-02	3.6E-02	2.0E-03
GSE5589_WT_VS_IL10_KO_LPS_AND_IL10_STIM_MACROPHAGE_45MIN_UP	4.5E-03	-	3.5E-02
GSE6259_BCELL_VS_CD8_TCELL_UP	2.6E-02	-	4.5E-03
GSE6674_UNSTIM_VS_ANTI_IGM_STIM_BCELL_UP	2.8E-02	-	1.0E-03
GSE7509_DC_VS_MONOCYTE_DN	4.9E-02	-	1.0E-03
GSE7509_UNSTIM_VS_TNFA_IL1B_IL6_PGE_STIM_DC_DN	3.4E-02	-	3.9E-02
GSE7768_OVA_ALONE_VS_OVA_WITH_MPL_IMMUNIZED_MOUSE_WHOLE_SPLEEN_6H_UP	6.0E-03	8.5E-03	-
GSE7852_LN_VS_FAT_TREG_DN	2.4E-02	2.9E-02	-
GSE8621_UNSTIM_VS_LPS_STIM_MACROPHAGE_DN	-	3.7E-02	3.1E-02
GSE8685_IL2_STARVED_VS_IL21_ACT_IL2_STARVED_CD4_TCELL_UP	2.4E-02	2.0E-02	-
GSE8921_3H_VS_24H_TLR1_2_STIM_MONOCYTE_UP	-	4.5E-03	4.2E-02
GSE8921_UNSTIM_VS_TLR1_2_STIM_MONOCYTE_24H_DN	-	2.7E-02	6.0E-03
GSE9037_WT_VS_IRAK4_KO_LPS_4H_STIM_BMDM_DN	1.0E-03	-	6.0E-03
GSE9988_ANTI_TREM1_VS_ANTI_TREM1_AND_LPS_MONOCYTE_DN	4.2E-02	1.5E-02	-
GSE9988_LPS_VS_VEHICLE_TREATED_MONOCYTE_UP	3.5E-02	4.0E-02	-
GUO_HEX_TARGETS_DN	4.5E-02	4.7E-02	2.4E-02
HALLMARK_UV_RESPONSE_UP	4.9E-02	-	3.7E-02
HU_GENOTOXIC_DAMAGE_24HR	4.8E-02	1.0E-02	-
HYDROLASE_ACTIVITY_ACTING_ON_ACID_ANHYDRIDES	2.0E-02	-	9.0E-03
HYDROLASE_ACTIVITY_ACTING_ON_CARBON_NITROGEN_NOT_PEPTIDEBONDS	-	4.5E-03	4.1E-02
HYDROLASE_ACTIVITY_ACTING_ON_CARBON_NITROGEN_NOT_PEPTIDEBONDSIN_LINEAR_AMIDES	-	9.0E-03	5.0E-04
INFLAMMATORY_RESPONSE	1.7E-02	2.7E-02	-
INTRACELLULAR_TRANSPORT	-	3.7E-02	4.1E-02
KEGG_FOCAL_ADHESION	2.5E-03	-	3.2E-02
KEGG_MAPK_SIGNALING_PATHWAY	1.5E-02	4.7E-02	-
KEGG_PATHWAYS_IN_CANCER	3.8E-02	4.9E-02	8.0E-03
KEGG_TIGHT_JUNCTION	5.0E-02	4.5E-02	-
KYNG_DNA_DAMAGE_UP	2.5E-02	2.5E-02	-
LEE_EARLY_T_LYMPHOCYTE_UP	1.1E-02	3.9E-02	-
LEE_LIVER_CANCER_E2F1_DN	4.4E-02	2.1E-02	-
LEE_LIVER_CANCER_MYC_E2F1_UP	2.0E-02	-	1.7E-02
LU_AGING_BRAIN_DN	3.6E-02	-	2.4E-02
MATZUK_MEIOTIC_AND_DNA_REPAIR	3.4E-02	3.4E-02	-
MEK_UP.V1_DN	4.3E-02	3.2E-02	-
MICROTUBULE_BASED_PROCESS	1.2E-02	-	4.3E-02
MIKKELSEN_MEF_LCP_WITH_H3K27ME3	2.0E-02	-	3.6E-02
MODULE_192	5.0E-04	-	6.5E-03
MODULE_195	1.1E-02	4.2E-02	1.7E-02
MODULE_279	5.0E-04	3.9E-02	3.0E-03
MODULE_289	-	1.9E-02	3.2E-02

(Continued)

Table i. (Continued)

Gene set name	p-value*		
	Forearm	**Femoral neck**	**Lumbar spine**
MODULE_334	1.0E-03	-	4.0E-03
MODULE_356	1.7E-02	-	3.2E-02
MODULE_427	1.0E-03	4.7E-02	3.0E-03
MODULE_480	5.0E-03	1.4E-02	1.4E-02
MODULE_97	4.4E-02	2.3E-02	-
MORF_DCC	-	2.7E-02	2.7E-02
NABA_ECM_GLYCOPROTEINS	4.1E-02	5.0E-02	2.8E-02
NIKOLSKY_BREAST_CANCER_16P13_AMPLICON	1.2E-02	5.0E-03	-
NUCLEOSIDE_TRIPHOSPHATASE_ACTIVITY	2.8E-02	-	1.2E-02
ORGANIC_ACID_TRANSPORT	1.7E-02	4.8E-02	-
PARK_TRETINOIN_RESPONSE_AND_RARA_PLZF_FUSION	1.0E-02	-	2.7E-02
PASINI_SUZ12_TARGETS_UP	2.5E-02	-	1.1E-02
PID_AR_NONGENOMIC_PATHWAY	3.2E-02	-	4.8E-02
PID_ECADHERIN_STABILIZATION_PATHWAY	3.3E-02	-	4.5E-02
PID_SYNDECAN_1_PATHWAY	2.3E-02	-	3.2E-02
PYROPHOSPHATASE_ACTIVITY	2.5E-02	-	2.0E-02
REACTOME_ACTIVATION_OF_NF_KAPPAB_IN_B_CELLS	-	3.6E-02	4.8E-02
REACTOME_CIRCADIAN_CLOCK	-	2.7E-02	1.0E-03
REACTOME_MAPK_TARGETS_NUCLEAR_EVENTS_MEDIATED_BY_MAP_KINASES	7.0E-03	2.1E-02	-
REACTOME_METABOLISM_OF_CARBOHYDRATES	4.2E-02	9.5E-03	-
REACTOME_MYOGENESIS	8.0E-03	1.7E-02	-
REACTOME_NCAM_SIGNALING_FOR_NEURITE_OUT_GROWTH	1.9E-02	-	2.8E-02
REACTOME_NEURONAL_SYSTEM	3.4E-02	-	3.1E-02
REACTOME_NUCLEAR_EVENTS_KINASE_AND_TRANSCRIPTION_FACTOR_ACTIVATION	6.0E-03	3.5E-02	-
REACTOME_RORA_ACTIVATES_CIRCADIAN_EXPRESSION	-	1.1E-02	5.0E-03
REACTOME_TRAF6_MEDIATED_INDUCTION_OF_NFKB_AND_MAP_KINASES_UPON_TLR7_8_OR_9_ACTIVATION	2.0E-03	3.2E-02	-
REACTOME_TRANSMEMBRANE_TRANSPORT_OF_SMALL_MOLECULES	4.6E-02	3.0E-03	-
REACTOME_TRANSMISSION_ACROSS_CHEMICAL_SYNAPSES	8.5E-03	-	1.3E-02
REACTOME_TRIF_MEDIATED_TLR3_SIGNALING	1.6E-02	3.2E-02	-
RESPONSE_TO_CHEMICAL_STIMULUS	-	3.3E-02	4.2E-02
ROVERSI_GLIOMA_COPY_NUMBER_UP	3.0E-03	-	2.0E-03
SARTIPY_BLUNTED_BY_INSULIN_RESISTANCE_DN	2.2E-02	-	4.1E-02
SEQUENCE_SPECIFIC_DNA_BINDING	-	9.5E-03	4.5E-03
TGACATY_UNKNOWN	2.7E-02	-	3.6E-02
TGGNNNNNNKCCAR_UNKNOWN	4.5E-03	-	1.6E-02
TSENG_IRS1_TARGETS_UP	-	2.5E-02	2.3E-02
V$CRX_Q4	3.2E-02	-	3.3E-02
V$GATA1_04	5.0E-03	-	4.7E-02
V$HNF4_01	2.5E-03	-	2.9E-02
V$SREBP1_Q6	4.2E-02	-	5.0E-04
V$SRF_Q5_01	2.3E-02	-	3.8E-02
V$TAL1BETAE47_01	1.9E-02	3.5E-03	-
V$TCF4_Q5	3.0E-02	-	2.5E-02
V$TEF1_Q6	4.5E-02	-	1.4E-02
VALK_AML_WITH_EVI1	3.1E-02	-	4.4E-02
WEIGEL_OXIDATIVE_STRESS_BY_HNE_AND_TBH	3.2E-02	-	5.0E-03
WELCH_GATA1_TARGETS	8.5E-03	-	1.5E-02
YAGI_AML_FAB_MARKERS	3.7E-02	8.0E-03	-
YTTCCNNNGGAMR_UNKNOWN	2.0E-03	3.7E-02	3.2E-02

*Kolmogorov-Smirnov running sum statistics was used and p-values were decided based on permutation[9]

Table ii. Methylation quantitative trait loci (meQTLs)-based gene set enrichment analysis results.

Gene set name	p-value*		
	Forearm	Femoral neck	Lumbar spine
ACAACCT,MIR-453	-	3.0E-03	3.1E-02
ANDROGEN_RECEPTOR_SIGNALING_PATHWAY	4.7E-02	-	3.4E-02
ANION_TRANSPORT	9.5E-03	-	1.1E-02
BIOCARTA_CLASSIC_PATHWAY	1.4E-02	-	2.8E-02
BIOCARTA_IL1R_PATHWAY	-	5.0E-02	2.7E-02
BIOCARTA_LAIR_PATHWAY	-	1.0E-02	1.6E-02
BRUECKNER_TARGETS_OF_MIRLET7A3_DN	2.8E-02	-	3.7E-02
CHANG_CYCLING_GENES	3.8E-02	1.0E-02	9.5E-03
chr6q14	2.6E-02	6.5E-03	3.0E-02
chr8p23	4.9E-02	-	5.0E-04
CTCTAGA,MIR-526C,MIR-518F,MIR-526A	2.6E-02	3.8E-02	-
DEMAGALHAES_AGING_UP	4.9E-02	4.2E-02	-
DIGESTION	-	4.6E-02	9.5E-03
DUAN_PRDM5_TARGETS	2.3E-02	-	4.6E-02
E2F1_UP.V1_UP	-	2.0E-02	2.3E-02
ESTABLISHMENT_OF_ORGANELLE_LOCALIZATION	3.5E-02	1.5E-02	-
FERRANDO_T_ALL_WITH_MLL_ENL_FUSION_DN	1.1E-02	-	2.5E-02
GCCNNNWTAAR_UNKNOWN	-	1.4E-02	4.0E-02
GCTCTTG,MIR-335	2.5E-02	2.5E-03	-
GGARNTKYCCA_UNKNOWN	2.5E-02	-	1.2E-02
GNF2_CCNA2	2.4E-02	4.5E-03	-
GNF2_H2AFX	3.7E-02	1.3E-02	-
GNF2_KISS1	4.3E-02	4.9E-02	1.3E-02
GNF2_MMP11	3.2E-02	4.3E-02	1.3E-02
GNF2_PCNA	4.0E-03	3.2E-02	-
GNF2_RRM1	2.8E-02	4.0E-02	-
GNF2_RRM2	4.0E-03	2.2E-02	-
GNF2_TTK	3.5E-02	1.1E-02	-
GSE11057_NAIVE_VS_CENT_MEMORY_CD4_TCELL_DN	4.1E-02	3.5E-02	-
GSE14769_UNSTIM_VS_240MIN_LPS_BMDM_UP	3.0E-02	-	1.3E-02
GSE15330_WT_VS_IKAROS_KO_GRANULOCYTE_MONOCYTE_PROGENITOR_UP	-	9.0E-03	1.9E-02
GSE17974_CTRL_VS_ACT_IL4_AND_ANTI_IL12_0.5H_CD4_TCELL_UP	1.9E-02	2.8E-02	-
GSE18893_CTRL_VS_TNF_TREATED_TREG_24H_DN	3.0E-02	-	1.5E-02
GSE1925_CTRL_VS_IFNG_PRIMED_MACROPHAGE_3H_IFNG_STIM_DN	-	4.5E-03	4.4E-02
GSE19772_CTRL_VS_HCMV_INF_MONOCYTES_UP	-	9.5E-03	2.3E-02
GSE21063_3H_VS_16H_ANTI_IGM_STIM_BCELL_DN	3.6E-02	-	3.7E-02
GSE21063_WT_VS_NFATC1_KO_8H_ANTI_IGM_STIM_BCELL_UP	3.0E-03	2.5E-03	-
GSE21379_TFH_VS_NON_TFH_CD4_TCELL_UP	2.2E-02	-	1.9E-02
GSE22886_CD8_VS_CD4_NAIVE_TCELL_DN	-	2.0E-03	4.0E-02
GSE23925_DARK_ZONE_VS_NAIVE_BCELL_DN	1.9E-02	1.3E-02	-
GSE25085_FETAL_LIVER_VS_ADULT_BM_SP4_THYMIC_IMPLANT_DN	1.9E-02	3.1E-02	-
GSE25088_CTRL_VS_ROSIGLITAZONE_STIM_MACROPHAGE_UP	-	1.0E-02	3.0E-03
GSE25123_CTRL_VS_IL4_STIM_MACROPHAGE_UP	-	3.1E-02	2.0E-03
GSE2585_CTEC_VS_MTEC_THYMUS_UP	4.1E-02	4.0E-02	-
GSE2826_WT_VS_XID_BCELL_DN	-	7.5E-03	3.0E-02
GSE29614_CTRL_VS_DAY3_TIV_FLU_VACCINE_PBMC_DN	2.1E-02	-	4.8E-02
GSE29618_PRE_VS_DAY7_POST_TIV_FLU_VACCINE_PDC_DN	3.1E-02	1.2E-02	-
GSE30962_PRIMARY_VS_SECONDARY_ACUTE_LCMV_INF_CD8_TCELL_UP	1.1E-02	3.3E-02	-
GSE36392_EOSINOPHIL_VS_MAC_IL25_TREATED_LUNG_UP	-	7.5E-03	5.0E-02
GSE3982_MAST_CELL_VS_NKCELL_DN	-	1.1E-02	1.5E-02
GSE41867_DAY8_VS_DAY15_LCMV_ARMSTRONG_EFFECTOR_CD8_TCELL_UP	1.7E-02	-	1.8E-02
GSE41867_NAIVE_VS_DAY8_LCMV_CLONE13_EFFECTOR_CD8_TCELL_DN	1.7E-02	2.5E-02	-
GSE42088_2H_VS_24H_LEISHMANIA_INF_DC_DN	-	1.4E-02	2.5E-02
GSE43863_DAY6_EFF_VS_DAY150_MEM_LY6C_INT_CXCR5POS_CD4_TCELL_DN	-	2.5E-03	2.5E-02
GSE43863_NAIVE_VS_LY6C_INT_CXCR5POS_CD4_EFF_TCELL_D6_LCMV_DN	7.0E-03	-	4.0E-02
GSE43955_1H_VS_60H_ACT_CD4_TCELL_UP	-	1.9E-02	2.4E-02
GSE45365_WT_VS_IFNAR_KO_CD8A_DC_UP	-	5.0E-02	5.0E-02
GSE7460_WT_VS_FOXP3_HET_ACT_WITH_TGFB_TCONV_UP	-	3.0E-02	4.6E-02
GSE7768_OVA_WITH_LPS_VS_OVA_WITH_MPL_IMMUNIZED_MOUSE_WHOLE_SPLEEN_6H_UP	3.0E-02	3.0E-02	-
GSE9960_GRAM_NEG_VS_GRAM_NEG_AND_POS_SEPSIS_PBMC_UP	-	4.8E-02	3.3E-02
HALLMARK_APICAL_JUNCTION	1.3E-02	3.9E-02	-
HALLMARK_MITOTIC_SPINDLE	5.0E-02	4.5E-03	-
IIZUKA_LIVER_CANCER_PROGRESSION_L0_L1_DN	3.0E-02	5.5E-03	-
INSULIN_LIKE_GROWTH_FACTOR_RECEPTOR_BINDING	-	5.0E-04	2.6E-02
KAECH_DAY8_EFF_VS_DAY15_EFF_CD8_TCELL_UP	1.9E-02	2.1E-02	-
KANG_DOXORUBICIN_RESISTANCE_UP	1.0E-02	8.0E-03	-
KARLSSON_TGFB1_TARGETS_UP	1.4E-02	-	4.9E-02

(Continued)

Table ii. (Continued)

Gene set name	p-value*		
	Forearm	**Femoral neck**	**Lumbar spine**
KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION	2.3E-02	6.0E-03	-
KOKKINAKIS_METHIONINE_DEPRIVATION_96HR_DN	1.4E-02	-	1.0E-02
KORKOLA_YOLK_SAC_TUMOR_UP	4.9E-02	-	4.5E-02
KRAS.AMP.LUNG_UP.V1_UP	-	4.8E-02	3.6E-02
LEE_AGING_NEOCORTEX_DN	4.5E-02	-	4.0E-03
LENAOUR_DENDRITIC_CELL_MATURATION_DN	4.7E-02	-	4.4E-02
LU_IL4_SIGNALING	-	4.9E-02	4.0E-02
MODULE_147	2.7E-02	6.0E-03	-
MODULE_256	3.4E-02	5.0E-03	-
MODULE_451	-	4.7E-02	2.0E-02
MORF_FDXR	4.4E-02	5.0E-04	-
MYLLYKANGAS_AMPLIFICATION_HOT_SPOT_12	-	2.9E-02	2.7E-02
NAKAMURA_ADIPOGENESIS_LATE_DN	-	3.3E-02	4.6E-02
NOUZOVA_METHYLATED_IN_APL	3.7E-02	1.2E-02	-
ORGANELLE_LOCALIZATION	-	2.5E-03	3.0E-02
OSWALD_HEMATOPOIETIC_STEM_CELL_IN_COLLAGEN_GEL_DN	-	4.2E-02	3.6E-02
PROTEIN_COMPLEX_BINDING	3.5E-03	3.3E-02	-
PUJANA_BREAST_CANCER_LIT_INT_NETWORK	1.0E-02	-	3.5E-02
RADAEVA_RESPONSE_TO_IFNA1_UP	3.6E-02	-	4.4E-02
RAMPON_ENRICHED_LEARNING_ENVIRONMENT_LATE_UP	-	5.0E-02	2.6E-02
REACTOME_AMINE_COMPOUND_SLC_TRANSPORTERS	-	4.6E-02	2.8E-02
REACTOME_FANCONI_ANEMIA_PATHWAY	-	6.0E-03	2.8E-02
REACTOME_GROWTH_HORMONE_RECEPTOR_SIGNALING	-	1.5E-02	4.4E-02
REACTOME_HYALURONAN_METABOLISM	6.0E-03	-	2.0E-03
REACTOME_HYALURONAN_UPTAKE_AND_DEGRADATION	1.6E-02	-	3.0E-03
REACTOME_LOSS_OF_NLP_FROM_MITOTIC_CENTROSOMES	5.5E-03	7.5E-03	-
REACTOME_RECRUITMENT_OF_MITOTIC_CENTROSOME_PROTEINS_AND_COMPLEXES	4.0E-03	1.1E-02	-
REACTOME_TRANSPORT_OF_VITAMINS_NUCLEOSIDES_AND_RELATED_MOLECULES	-	1.3E-02	1.0E-03
RODRIGUES_NTN1_AND_DCC_TARGETS	-	4.2E-02	3.4E-02
SPINDLE_POLE	4.6E-02	-	4.9E-02
SPIRA_SMOKERS_LUNG_CANCER_UP	-	4.8E-02	4.1E-02
TRANSCRIPTION_COACTIVATOR_ACTIVITY	-	4.4E-02	3.1E-02
UROSEVIC_RESPONSE_TO_IMIQUIMOD	-	4.9E-02	4.8E-02
V$CREB_Q4	-	3.6E-02	4.5E-03
V$E2F_03	1.3E-02	-	1.4E-02
V$E2F_Q3	4.0E-03	-	2.0E-03
V$E2F_Q3_01	7.0E-03	-	1.5E-03
V$E2F_Q4_01	1.7E-02	-	3.0E-03
V$E2F1_Q3	1.3E-02	4.9E-02	-
V$E2F1_Q4_01	5.0E-03	-	1.5E-03
V$FREAC7_01	3.5E-03	3.4E-02	-
VALK_AML_CLUSTER_6	2.2E-02	8.0E-03	-
VERRECCHIA_RESPONSE_TO_TGFB1_C4	5.5E-03	-	8.5E-03
WHITFIELD_CELL_CYCLE_S	9.5E-03	1.6E-02	-
ZHAN_MULTIPLE_MYELOMA_PR_UP	4.7E-02	1.1E-02	-
ZHANG_ANTIVIRAL_RESPONSE_TO_RIBAVIRIN_UP	-	4.1E-02	4.6E-02
ZHANG_TLX_TARGETS_60HR_DN	-	4.5E-02	4.4E-02

*Kolmogorov-Smirnov running sum statistics was used and p-values were decided based on permutation[9]

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