

Supplementary information

DNA Methylation Predicts Adverse Outcomes of Coronary Artery Disease

Min Qin^{1,2,3,4,5,6†}, Xiaoxue Tian^{1,2,7†}, Qili Wu^{1,2}, Qian Zhu^{1,2}, Meiling Yu^{1,2,8},
Xianhong Fang⁹, Xiaoping Chen¹⁰, Chen Liu¹¹, Bin Zhang⁹, Hanping Li², Xipei
Wang¹², Cuiping Pan^{6,13*}, Shilong Zhong^{1,2,12*}

Affiliations:

¹Department of Pharmacy, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University; Guangzhou, China.

²Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University; Guangzhou, China.

³School of Medicine, South China University of Technology; Guangzhou, China.

⁴Department of Pharmacy, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China.

⁵Laboratory of Phase I Clinical Trials, Medical Research Center of Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University; Guangzhou, China.

⁶Center for Intelligent Medicine Research, Greater Bay Area Institute of Precision Medicine (Guangzhou); Guangzhou, China.

⁷School of Pharmaceutical Science & Yunnan Key Laboratory of Pharmacology for Natural Products, Kunming Medical University, Kunming 650500, China.

⁸Department of Pharmacy, The First Affiliated Hospital of Bengbu Medical University, 287 Changhuai Road, Bengbu, Anhui, 233004, P.R. China.

⁹Department of Cardiology, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University; Guangzhou, China.

¹⁰Department of Clinical Pharmacology, Xiangya Hospital, Central South University; Changsha, China.

¹¹Department of Cardiology, The First Affiliated Hospital of Sun Yat-Sen University; Guangzhou, China.

¹²Laboratory of Phase I Clinical Trials, Medical Research Center of Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University; Guangzhou, China.

¹³Bioscience and Biomedical Engineering Thrust, Systems Hub, The Hong Kong University of Science and Technology (Guangzhou); Guangzhou, China.

† These authors contributed equally to this work.

***Corresponding author**

Cuiping Pan: cuipingpan@hkust-gz.edu.cn

Shilong Zhong: gdph_zhongsl@gd.gov.cn and zhongsl@hotmail.com

Contents

Supplementary Fig. 1..... 4

Supplementary Fig. 2..... 5

Supplementary Fig. 3..... 6

Supplementary Fig. 4..... 7

Supplementary Fig. 5..... 8

Supplementary Fig. 6..... 9

Supplementary Fig. 7..... 10

Supplementary Fig. 8..... 11

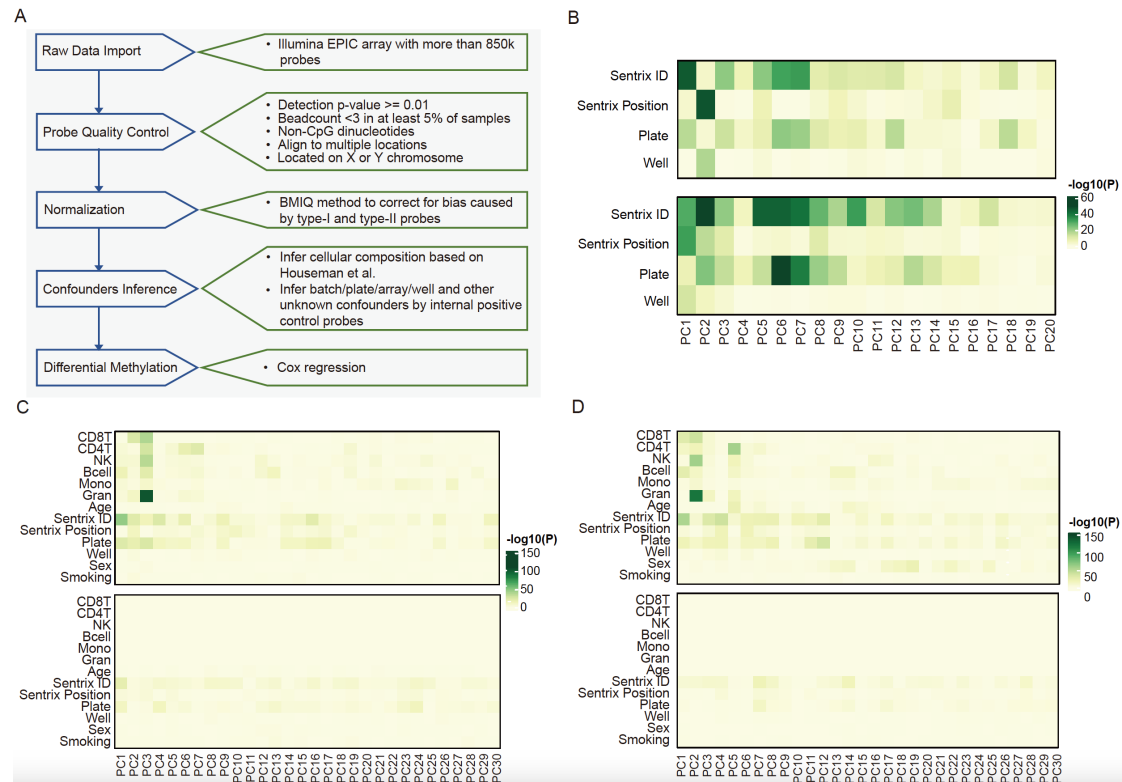
Supplementary Fig. 9..... 12

Supplementary Fig. 10 13

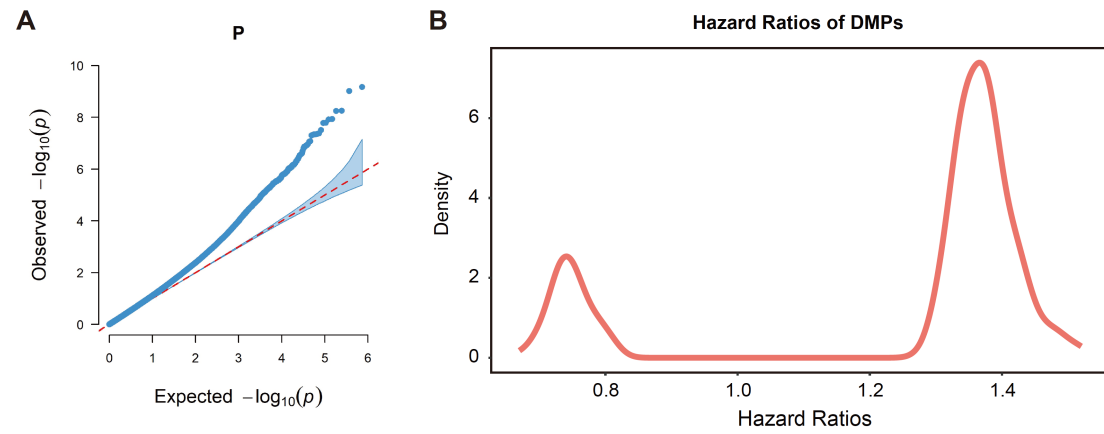
Supplementary Table 1. 14

Supplementary Table 2. 26

Supplementary Table 3. 28

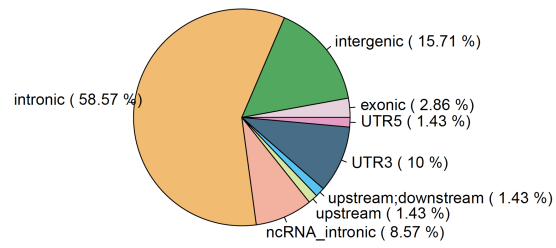


Supplementary Fig. 1 Quality control of the methylation probes in the discovery set. (A) Workflow to derive clean methylation probes. **(B)** Correlation between the batch information and the top 20 principal components of the methylation beta values from about 200 control probes in the discovery cohort (Upper) and validation cohort (Lower). **(C)** Correlation between the top 30 principal components of the methylation data versus cell components and batch information in the discovery cohort. About 730,000 methylation sites passing the previous QC steps were inputted for calculation. Upper: before the residual calculation. Lower: after the residual calculation. **(D)** Correlation between the top 30 principal components of the methylation data versus cell components and batch information in the validation cohort. The settings were the same as in the discovery cohort in **(C)**.

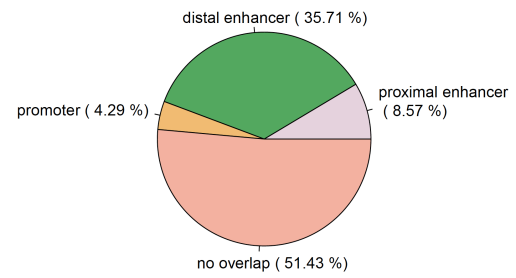


Supplementary Fig. 2 EWAS of death in the discovery set. (A) Quantile-quantile plot of the association P values. **(B)** Methylation beta values of the DMPs associated with death in CAD.

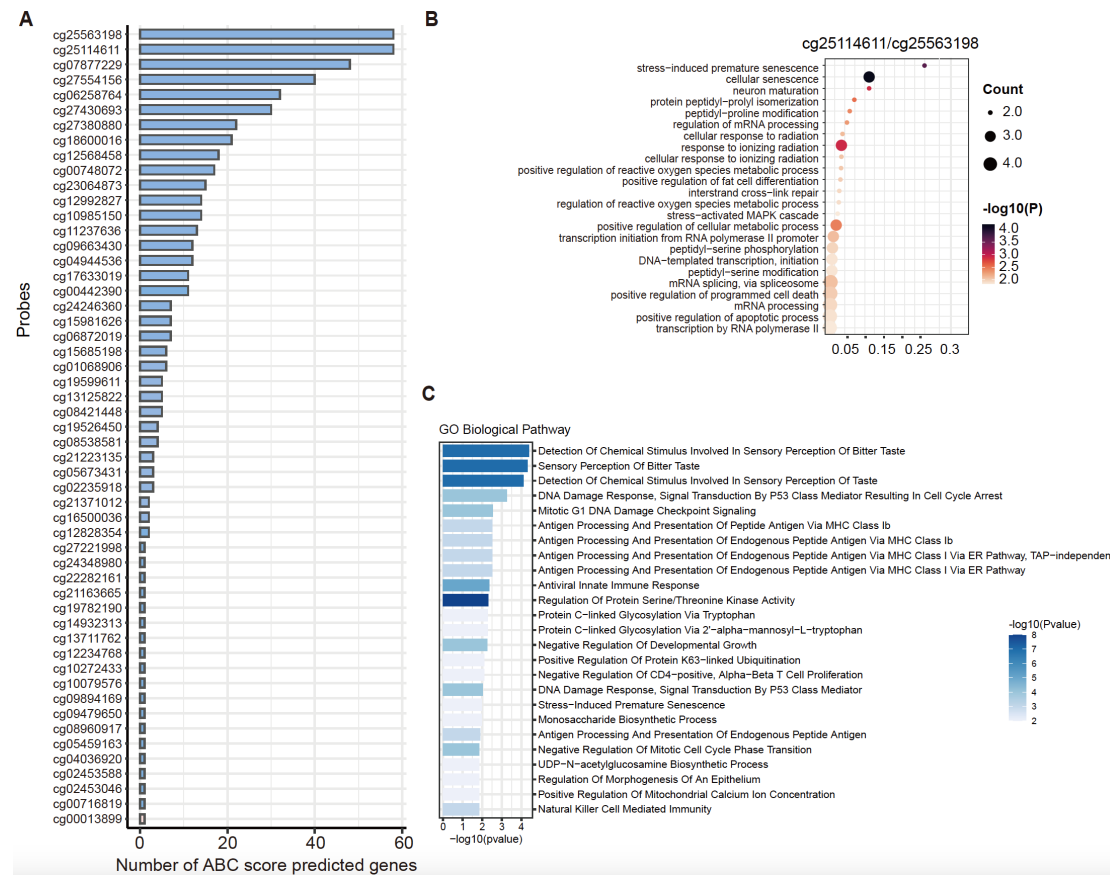
A



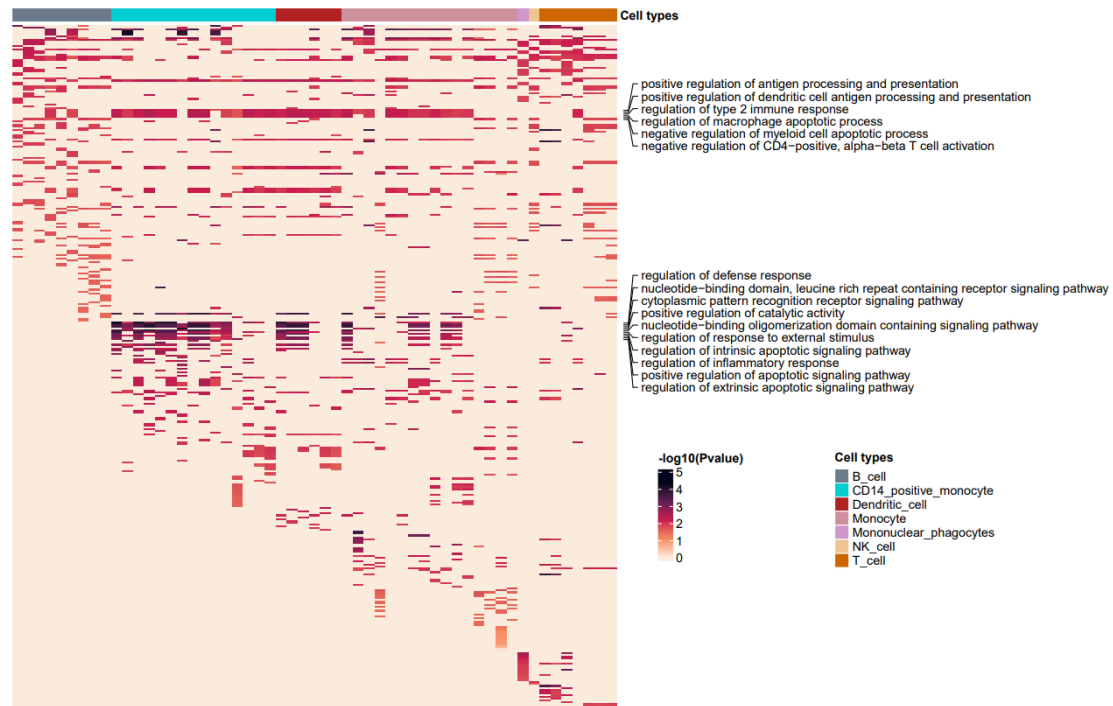
B



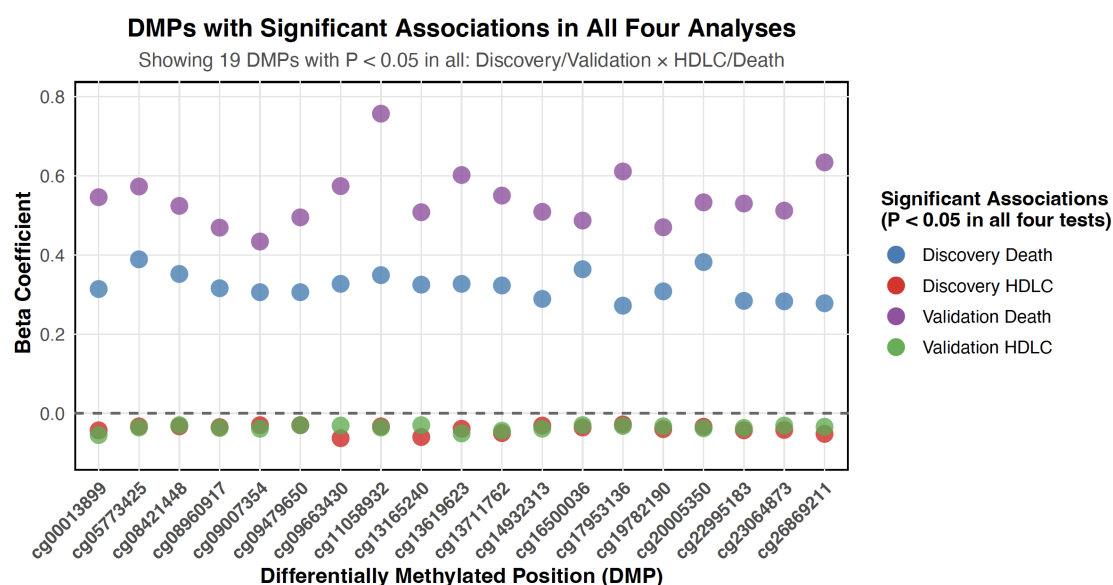
Supplementary Fig. 3 Genomic distribution of the 333 DMPs associated with future death in CAD. (a) Genic regions. (b) Overlap with enhancers and promoters.



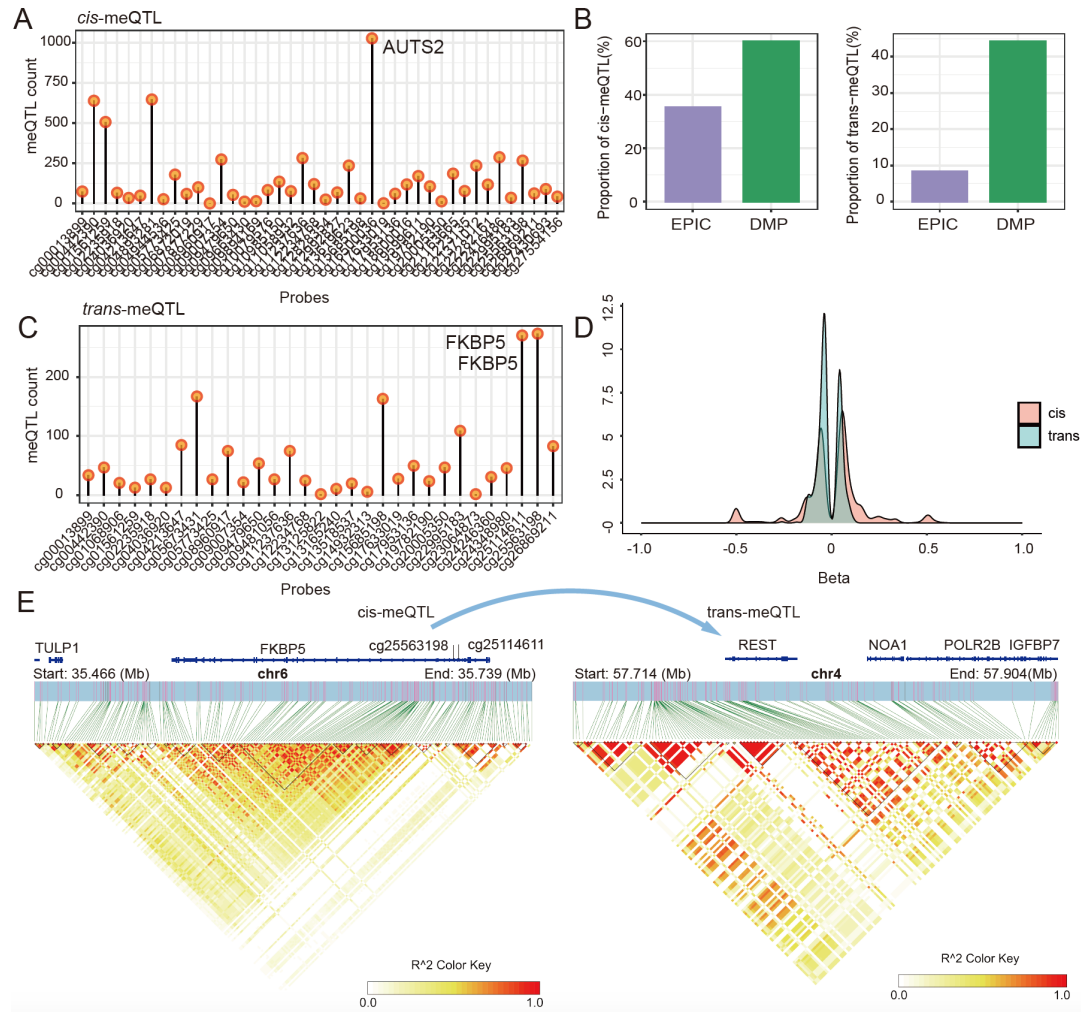
Supplementary Fig. 4 Target genes of DMPs predicted by the activity-by-contact (ABC) model. (A) Number of target genes derived from connecting DMPs (+/- 2500bp) to enhancers and then to target genes by the ABC model. **(B)** Pathway enrichment for the largest set of target genes identified from (A). Both DMPs, cg25114611 and cg25563198, were located on the same super-enhancer, which was predict by the ABC model to interaction with > 50 genes, forming the largest target gene set for the DMPs. **(C)** Pathway enrichment for the 468 genes predicted by ABC score.



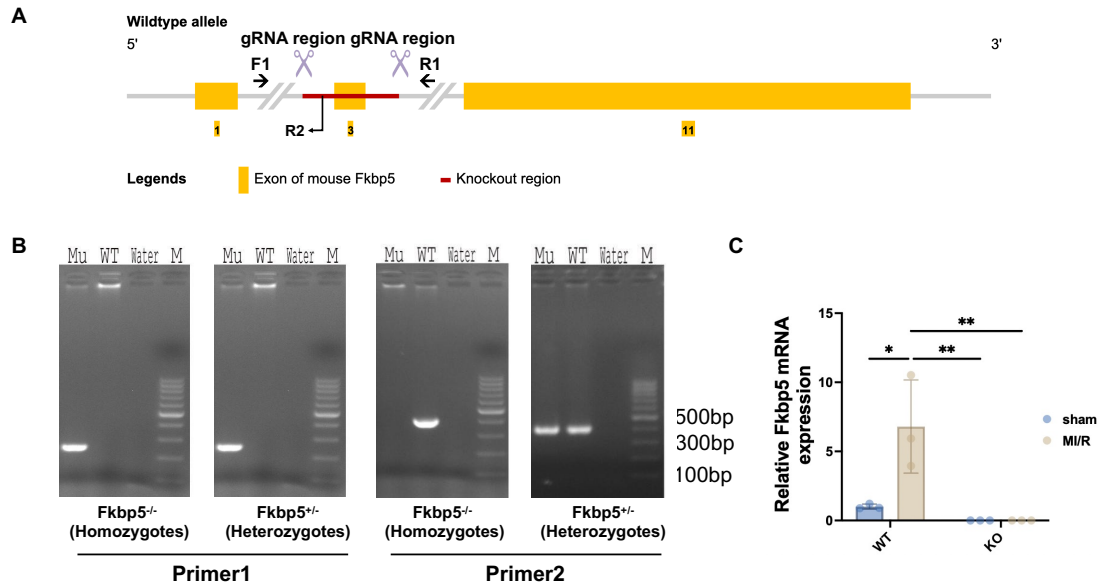
Supplementary Fig. 5 Pathway enrichment of the target genes of DMPs in blood cell types. Target genes were derived from mapping DMPs (+/- 2500bp) to enhancers then to target genes via the activity-by-contact model.



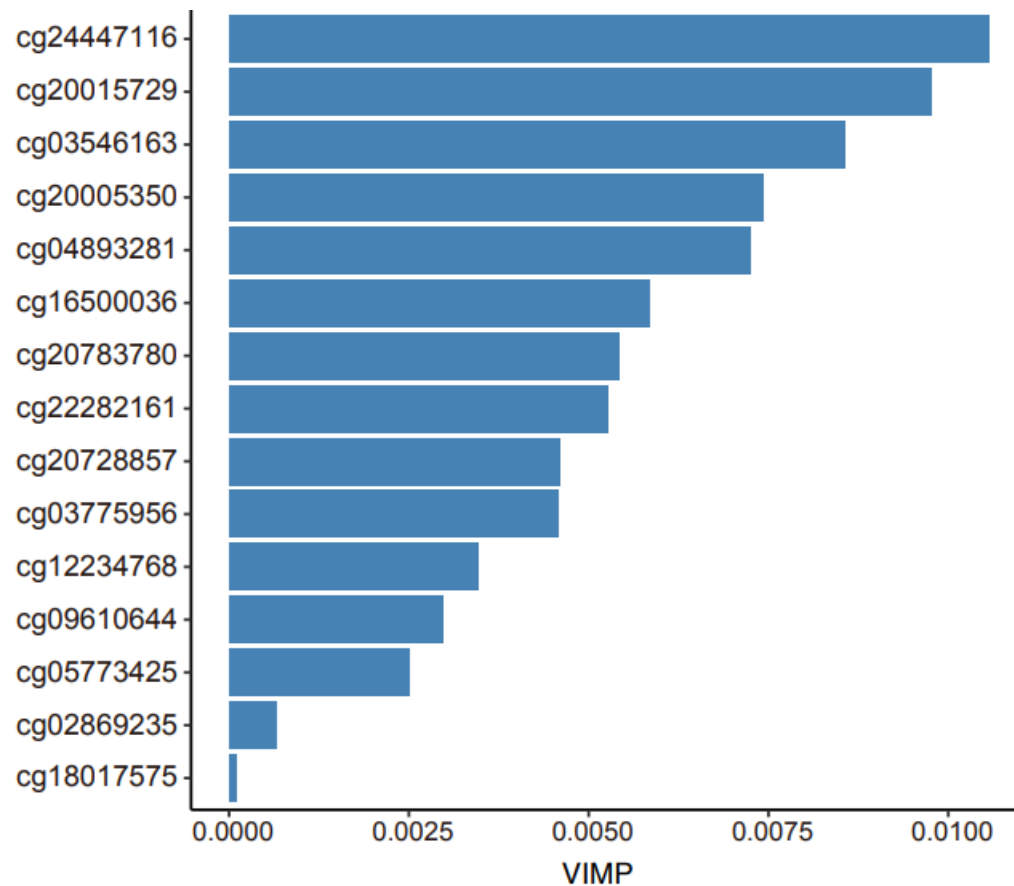
Supplementary Fig. 6 19 death-associated DMPs that are also significantly associated with HDLC levels in both the Discovery set and the Validation set. Scatter plots display beta coefficients for the associations between the DNA methylation of 70 death-associated DMPs and HDLC levels, across both discovery and validation datasets. Each dot represents one DMP. Red: Discovery HDLC; blue: Discovery Death; green: Validation HDLC; purple: Validation Death. Source data are provided as a Source Data file.



Supplementary Fig. 7 Genetic regulation of DMPs associated with death in CAD. (A) Number of *cis*-meQTLs associated with the DMPs. (B) Number of *trans*-meQTLs associated with the DMPs. (C) Proportion of CpGs having *cis*- and *trans*- meQTLs. (D) Association strength, beta, between the DMPs and the meQTLs. (E) meQTLs for two DMPs located on the promoter of *FKBP5* on chromosome 6, with cg25563198 associated with 267 *cis*-meQTLs on chromosome 6 (left) and 273 *trans*-meQTLs on chromosome 4 (right), and cg25114611 associated with 270 *trans*-meQTLs on chromosome 4 (right). Linkage disequilibrium between the meQTLs, as measured by R^2 , was indicated by the triangle plots. EPIC: all CpGs in the Infinium methylation array.

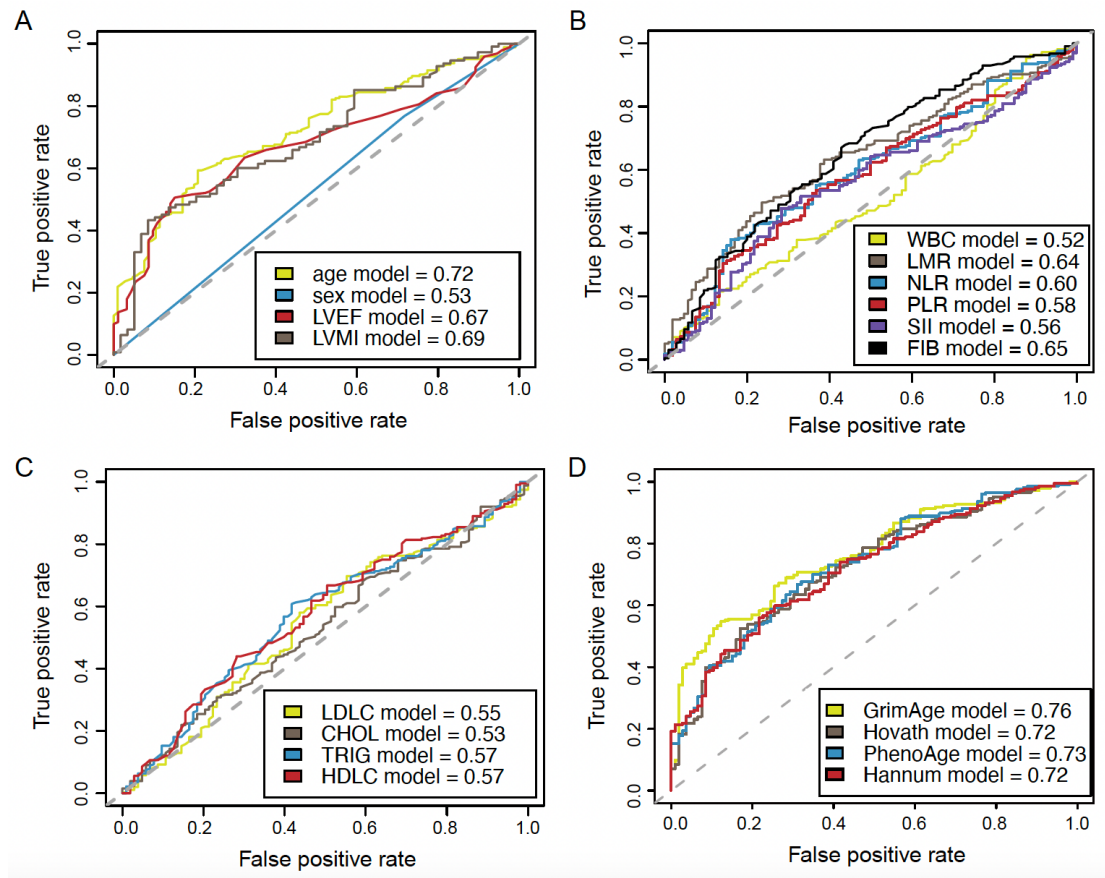


Supplementary Fig. 8 Schematic diagram of *Fkbp5* knockout mice and PCR results. (A) The schematic diagram of *Fkbp5* KO mice. (B) The PCR product of each primer in Homozygotes (*Fkbp5*^{-/-}) and Heterozygotes (*Fkbp5*^{+/-}) mice. (C) The mRNA expression of *Fkbp5* in WT and KO mice (n =3 for each group, N= 3 experiments, *P = 0.018, **P = 0.007).



Supplementary Fig. 9 Feature selection for the prognostic models of CAD.

15 DMPs were assessed by random survival forest for their contribution in predicting death. The top 10 DMPs with the largest variable importance (VIMP) were selected as features for modeling.



Supplementary Fig. 10 Prognostic models for CAD based on different clinical phenotypes and DNA methylation clocks. ROC curves were shown for models based on **(A)** sex, age, LVEF, and LVMI, **(B)** inflammation indices including WBC, PLR, NLR, PLR, SII, and FIB, **(C)** lipids including LDLC, CHOL, TRIG, and HDLC, and **(D)** methylation clocks including GrimAge, Hovath clock, PhenoAge clock, and Hannum clock. LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index, PLR: plate-lymphocyte ratio, FIB: fibrinogen, SII: systemic inflammation index, WBC: white blood cell count, LMR: lymphocyte-monocyte ratio, NLR: neutrophil-lymphocyte ratio, HDLC: high-density lipoprotein cholesterol, LDLC: low-density lipoprotein cholesterol, CHOL: total cholesterol, TRIG: triglycerides.

Supplementary Table 1. Relationships between prognosis-associated DMPs and traits in previous reported studies and mediating phenotypes

Probes	CHR	POS	Gene	Associated traits in EWAS Catalogue and EWAS Atalas
cg10759293	20	19999226	NAA20	Kabuki syndrome (KS); air pollution (NO2)
cg20710824	17	80560593	FOXK2	breastfeeding
				Crohn's disease; B Acute Lymphoblastic Leukemia with t(12; 21)(p13.2; q22.1); ETV6-
cg12658897	11	60918586	VPS37C	RUNX1; alcohol consumption; breast cancer prognosis; thoracic ossification of the ligamentum flavum
cg18978606	2	104996948	NA	air pollution (Pb); smoking; eosinophilia
cg00005893	6	158508543	SYNJ2	
cg08941570	11	101815129	CEP126	
cg14779218	19	13925420	ZSWIM4	
cg01499619	5	179205250	NA	eosinophilia
cg04213647	13	99499944	DOCK9	ancestry
cg05645211	10	27112649	ABI1	polychlorinated biphenyls (PCBs) exposure
cg09272951	5	139926789	EIF4EBP3; ANKHD1-EIF4EBP3	gingivo-buccal oral squamous cell carcinoma (OSCC-GB)
cg10040821	12	99193806	ANKS1B	asthma
cg18017575	7	75213863	HIP1	Downs Syndrome; Crohn's disease
cg21786381	11	75234078	GDPD5	atopy; atopic dermatitis; air pollution (NO2)
cg15369596	3	197260526	BDH1	
cg08960917	9	127114588	NEK6	
cg02013655	22	18390007	MICAL3	
cg13237094	2	37771327	NA	
cg10136671	7	142557703	EPHB6	
cg15522298	9	33168523	B4GALT1; B4GALT1-AS1	
cg20005350	5	111478628	NA	
cg14082886	11	35164485	CD44	systemic lupus erythematosus (SLE); atopy
cg22416486	15	79704442	NA	Crohn's disease
cg26352490	12	10342643	TMEM52B	Smoking
cg27380880	12	65022110	RASSF3	
cg24348980	1	232073393	DISC1-IT1; DISC1	
cg18894545	4	42281051	NA	
cg21977847	12	42484384	GXYLT1	
cg00766374	2	202833575	NA	
cg12004045	11	20071710	NAV2-AS2; NAV2	Crohn's disease
				atopy; gestational age; waist circumference (WC); body mass index (BMI); alcohol consumption
cg13139542	2	8242815	NA	

cg05459163	14	92411904	FBLN5	Crohn's disease
cg10705487	5	179108352	CBY3	Crohn's disease
cg27365342	6	12881417	PHACTR1	smoking; Crohn's disease; Alzheimer disease (AD); multiple sclerosis
cg18097436	15	71763927	THSD4	
cg18140642	1	236094805	NA	
cg03331035	8	135813886	MIR30B	air pollution (Pb); eosinophilia; asthma; obesity; preterm birth
cg10327647	1	192914734	LINC01032	
cg00522231	2	9549277	ITGB1BP1	aging; smoking; down syndrome; mortality
cg07655126	1	236019440	LYST	eosinophilia
cg07768118	2	8280378	LINC00299	alcohol withdrawal recovery
cg01212284	3	182814959	MCCC1	systemic lupus erythematosus (SLE); Kabuki syndrome (KS); maternal depression; air pollution (NO2)
cg07711192	12	14426994	NA	smoking; oral squamous cell carcinoma (OSCC)
cg17020524	1	13917231	PDPN	ancestry
cg24031137	5	148939617	NA	smoking; fractional exhaled nitric oxide
cg13461821	8	97280827	PTDSS1	
cg08923594	1	7462176	CAMTA1	papillary thyroid carcinoma
cg10985150	6	150989765	PLEKHG1	
cg11358155	11	10746964	NA	
cg27304798	11	118095739	AMICA1	
cg02721155	4	125634496	ANKRD50	
cg02749012	3	134948139	EPHB1	
cg18647879	2	129207858	NA	
cg00013899	1	64992433	CACHD1	smoking; asthma; identify lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC)
cg16113254	14	75777372	NA	psoriasis; type 2 diabetes (T2D); allergic asthma
cg24686270	5	147281313	C5orf46	asthma
cg23509699	6	15756072	NA	
cg22447489	7	80873704	NA	
cg18303533	5	157702687	NA	lung cancer risk; lung cancer
cg11237636	10	126380541	FAM53B	
cg27128761	5	151055650	SPARC	sex; smoking; soluble tumor necrosis factor receptor 2 (sTNFR2) levels in plasma; Alzheimer disease (AD); Crohn's disease; fractional exhaled nitric oxide; down syndrome; type 2 diabetes (T2D); multiple sclerosis; breast cancer prognosis

cg16107565	11	62344917	TUT1	fractional exhaled nitric oxide; lifestyle scores (LS)
cg07514306	7	129934352	CPA4	
cg13085627	15	101597169	LRRK1	systemic lupus erythematosus (SLE); estimated glomerular filtration rate (eGFR); air pollution (NO2); fractional exhaled nitric oxide; down syndrome
cg14932313	14	25043420	CTSG	air pollution (NO2); allergic sensitization
cg00131893	8	1892956	ARHGEF10	smoking; down syndrome; preeclampsia
cg20783780	11	112191546	LOC283140	Gulf War Illness
cg23551432	8	119154786	NA	fractional exhaled nitric oxide
cg00716819	10	71882625	AIFM2	
cg06897548	22	39810706	TAB1	myalgic encephalomyelitis/chronic fatigue syndrome; high risk cutaneous squamous cell carcinoma (cSCC)
cg01068906	16	50745944	NOD2	aging
cg27430693	12	94208276	CRADD	
cg19526450	5	142254301	ARHGAP26	
cg12234768	2	88862824	LOC101928371; EIF2AK3	ancestry
cg02869235	12	124726864	NA	thyroid lesion; smoking; mixed connective tissue disease (MCTD); follicular thyroid carcinoma; malignant pleural mesothelioma; estimated glomerular filtration rate (eGFR); Crohn's disease; mortality; fractional exhaled nitric oxide; air pollution (NO2); multiple sclerosis
cg12992827	3	101901234	NA	systemic lupus erythematosus (SLE); inflammatory bowel disease; adenoma; body mass index (BMI); body mass index (BMI) change; Crohn's disease; death risk; cognitive function; down syndrome; atopy; maternal alcohol consumption; aging
cg20000602	12	124733846	NA	aging; gestational age; eosinophilia; Kabuki syndrome (KS); atopy; preterm birth
cg07623341	14	68288913	RAD51B	glucocorticoid exposure
cg13673960	4	1742301	TACC3	preterm birth; multiple sclerosis
cg20674727	11	116761492	SIK3	Crohn's disease
cg02584791	13	31772717	B3GLCT	
cg09481056	16	2339260	ABCA3	soluble tumor necrosis factor receptor 2 (sTNFR2) levels in plasma; smoking; alcohol consumption
cg23598089	1	203652079	ATP2B4	schizophrenia; psychosis; Crohn's disease; atopy

cg25498638	6	7996863	BLOC1S5-TXNDC5	smoking; fractional exhaled nitric oxide
cg17918753	7	151561094	PRKAG2	myalgic encephalomyelitis/chronic fatigue syndrome
cg05382012	16	67517841	AGRP	systemic lupus erythematosus (SLE); allergic sensitization; preeclampsia; air pollution (NO2); air pollution (PM2.5); fractional exhaled nitric oxide; maternal depression; perinatally-acquired HIV; multiple sclerosis
cg08195491	16	50746063	NOD2	oral squamous cell carcinoma (OSCC)
cg09076900	7	107745087	LAMB4	atopy
cg14898243	10	70863693	SRGN	Kabuki syndrome (KS)
cg15407091	5	148211186	NA	down syndrome; polybrominated biphenyl exposure
cg23509724	2	210316331	MAP2	air pollution (Na)
cg26286606	19	19654180	CILP2	eosinophilia
cg21371012	8	119269219	SAMD12	
cg25799293	20	50349394	ATP9A	
cg21782900	3	194806364	XXYLT1	
cg13128137	1	36635209	MAP7D1	
cg22347637	2	40467425	SLC8A1-AS1; SLC8A1	
cg05140524	9	111025632	NA	
cg01977883	6	15501554	JARID2	
cg18600016	8	95772595	DPY19L4	
cg08771569	2	214090794	NA	
cg26479002	16	19753559	IQCK	
cg14926258	8	109019743	RSPO2	
cg20088478	1	180984104	STX6	
cg05309081	17	15990620	NCOR1	
cg04917472	20	57583286	CTSZ	
cg02453046	21	17210173	USP25	Cancer treatment: chest-RT
cg07594341	4	24809415	CCDC149	preterm birth
cg26102435	14	99507062	NA	smoking
cg26799820	1	145089017	NA	
cg00010572	2	8345013	LINC00299	
cg25426982	18	61683198	NA	
cg03388121	16	66692404	CMTM4	Lifetime PTSD
cg07624918	3	136533970	NA	adenoma; eosinophilia; atopy; perinatally-acquired HIV; down syndrome; allergic sensitization
cg06258764	10	73510169	C10orf54; CDH23	ancestry; end-stage kidney disease attributed to diabetic kidney disease; myalgic encephalomyelitis/chronic fatigue syndrome
cg00748072	2	174862824	NA	papillary thyroid carcinoma; birth weight; air pollution (NO2); multiple sclerosis

cg15773890	6	17259549	NA	alcohol consumption; perinatally-acquired HIV; smoking; vitamin B12 supplement; allergic sensitization
cg17323179	1	52747420	ZFYVE9	
cg22959742	10	13913931	FRMD4A	soluble tumor necrosis factor receptor 2 (sTNFR2) levels in plasma; chemotherapy for breast cancer; kidney disease; multiple sclerosis
cg11169848	11	67142030	LOC100130987; CLCF1	systemic lupus erythematosus (SLE); colorectal cancer; papillary thyroid carcinoma; colorectal laterally spreading tumor; down syndrome; Gulf War Illness; oral squamous cell carcinoma (OSCC); hepatocellular carcinoma (HCC); multiple sclerosis
cg04595884	17	58870064	BCAS3	cell-specific characterization of the placental methylome
cg09663430	22	18251942	BID	Crohn's disease
cg24495681	8	121186838	COL14A1	aging; atopy; birth weight; maternal smoking
cg13412579	12	116398830	MED13L	down syndrome; Papuan ancestry
cg04944536	12	116756890	NA	air pollution (Na); smoking; air pollution (Pb); schizophrenia; alcohol consumption
cg12670943	22	43006541	POLDIP3	alcohol consumption; Crohn's disease
cg03067296	17	76274577	LOC100996291	Crohn's disease; Body mass index; Waist Circumference; down syndrome; Smoking; aging; C-reactive protein;
cg05773425	1	16644480	FBXO42	Crohn's disease
cg09610644	3	197249274	BDH1	estimated glomerular filtration rate (eGFR); soluble tumor necrosis factor receptor 2 (sTNFR2) levels in plasma; alcohol withdrawal recovery; Crohn's disease; kidney disease; hormone therapy
cg20015729	3	23430728	UBE2E2; MIR548AC	myalgic encephalomyelitis/chronic fatigue syndrome
cg26869211	17	58309224	SCARNA20; USP32	Smoking
cg22775635	6	6851367	NA	
cg13619623	7	33637324	BBS9	alcohol consumption
cg05165263	4	185317227	IRF2	end-stage kidney disease attributed to diabetic kidney disease; Crohn's disease; ancestry; estimated glomerular filtration rate (eGFR)
cg20728857	4	1359138	UVSSA	
cg07768696	17	55676682	MSI2	eosinophilia; atopy
cg04893281	10	97732939	ENTPD1-AS1	
cg23063370	5	132601937	FSTL4	

cg02543993	7	5736195	RNF216	eosinophilia; Crohn's disease; atopy; smoking; estimated glomerular filtration rate (eGFR); fractional exhaled nitric oxide; breast cancer prognosis
cg19782190	14	103487004	CDC42BPB	atopy; malignant pleural mesothelioma; fractional exhaled nitric oxide
cg08538581	1	162500634	NA	eosinophilia; Hyperdiploid B Acute Lymphoblastic Leukemia
cg13074526	17	76274743	LOC100996291	Crohn's disease; aging
cg16217672	10	75843201	VCL	down syndrome
cg23089177	7	30196932	MTURN	down syndrome
cg25132241	14	92396859	FBLN5	smoking; soluble tumor necrosis factor receptor 2 (sTNFR2) levels in plasma; Crohn's disease; multiple sclerosis; high risk cutaneous squamous cell carcinoma (cSCC)
cg03775956	12	124656418	ZNF664-FAM101A	Crohn's disease; FEV1; lung function; preterm birth; Coagulation factor VIII; Body mass index; FVC; gestational diabetes mellitus; a lifestyle intervention in pregnant women with obesity; 1-hour glucose; aging
cg14911380	15	59181722	SLTM	
cg19748455	17	76274856	LOC100996291	Crohn's disease
cg22282161	7	21590890	DNAH11	Crohn's disease
cg12828354	5	149466715	CSF1R	Crohn's disease
cg21805866	5	132602073	FSTL4	
cg17188688	22	22333247	TOP3B	
cg24830898	5	177964873	COL23A1	systemic lupus erythematosus (SLE); down syndrome; air pollution (NO2); multiple sclerosis
cg13801687	2	27426245	SLC5A6	
cg15164272	1	236311362	GPR137B	
cg15685198	2	135163836	MGAT5	
cg07333021	6	30612330	C6orf134	systemic lupus erythematosus (SLE); soluble tumor necrosis factor receptor 2 (sTNFR2) levels in plasma; estimated glomerular filtration rate (eGFR); Crohn's disease; air pollution (NO2); smoking; preeclampsia; fractional exhaled nitric oxide; multiple sclerosis
cg09670127	2	60722802	BCL11A	inflammatory bowel disease; asthma; air pollution (NO2); myalgic encephalomyelitis/chronic fatigue syndrome
cg24538070	6	166649636	LOC101929297	
cg15469849	14	95981033	NA	

cg10827767	22	31794522	DRG1	systemic lupus erythematosus (SLE); atopy; kidney disease; fractional exhaled nitric oxide
cg00475235	17	54236118	ANKFN1	
cg06731639	16	50699167	NA	down syndrome
cg16518729	17	80845575	TBCD	preeclampsia; exercise
cg21163665	12	124657078	ZNF664-FAM101A	
cg17633019	7	143015959	CLCN1	
cg09711214	11	12924825	TEAD1	
cg21223135	6	149320810	UST	
cg21678211	12	56863261	SPRYD4	
cg18835596	6	135540107	MYB	eosinophilia; atopy; birth weight; alcohol consumption; perinatally-acquired HIV; ankylosis spondylitis (AS); air pollution (NO2); smoking; down syndrome
cg24246360	6	82954226	IBTK	Kabuki syndrome (KS); exercise; alcohol withdrawal recovery
cg25114611	6	35696870	FKBP5; LOC285847	systemic lupus erythematosus (SLE); inflammatory bowel disease; smoking; Crohn's disease; Acute myocardial infarction; Behcet disease; breast cancer; maternal smoking; death risk; gestational diabetes mellitus; preterm birth
cg03546163	6	35654363	FKBP5	systemic lupus erythematosus (SLE); end- stage kidney disease attributed to diabetic kidney disease; death risk; asthma; chemotherapy for breast cancer; malignant pleural mesothelioma; Behcet disease; down syndrome; mortality; Creutzfeldt-Jakob disease; primary Sjögren's Syndrome (pSS); aging
cg27554156	12	13248725	GSG1	atherosclerotic plaque; smoking; estimated glomerular filtration rate (eGFR); alcohol consumption
cg12271728	10	27772081	NA	oral glucose tolerance test
cg21819305	22	47226503	TBC1D22A	Smoking
cg20032949	17	35879117	SYNRG	
cg06872019	13	31588778	NA	aging; orofacial cleft; tic disorders
cg15845846	10	7659399	ITIH5	triiodothyronine (T3) treatment
cg08081361	6	1462092	NA	
cg17953136	2	20232577	LAPTM4A	smoking; Crohn's disease; fractional exhaled nitric oxide; ankylosis spondylitis (AS); down syndrome; allergic sensitization; myalgic encephalomyelitis/chronic fatigue syndrome
cg08421448	16	31106703	VKORC1	

cg00667851	10	44408164	LINC00841	
cg07560536	19	39739659	IFNL4	
cg00514199	11	125899758	CDON	eosinophilia
cg18844163	5	142362123	ARHGAP26	
cg20152841	19	2073190	MOBKL2A	Hyperdiploid B Acute Lymphoblastic Leukemia; Ischaemic stroke; preeclampsia; fractional exhaled nitric oxide; multiple sclerosis mixed connective tissue disease (MCTD); fractional exhaled nitric oxide; Type II diabetes mellitus; mammographic density measure; air pollution (NO2); down syndrome
cg22233512	17	55543388	MSI2	
cg03237401	1	193104672	MIR1278; CDC73	
cg24845511	15	101597093	LRRK1	alcohol withdrawal recovery; Papuan ancestry; estimated glomerular filtration rate (eGFR)
cg02908223	2	146569882	NA	fractional exhaled nitric oxide
cg21484914	16	2338842	ABCA3	fractional exhaled nitric oxide
cg22675732	2	145593773	TEX41	fractional exhaled nitric oxide aging; estimated glomerular filtration rate (eGFR); eosinophilia; kidney disease; smoking; soluble tumor necrosis factor receptor 2 (sTNFR2) levels in plasma; fractional exhaled nitric oxide; allergic sensitization; ankylosis spondylitis (AS); down syndrome; myalgic encephalomyelitis/chronic fatigue syndrome; Parkinson disease (PD); sepsis; severe sepsis fractional exhaled nitric oxide; perinatally- acquired HIV
cg04036920	11	33562503	C11orf41	
cg11058932	7	130372167	TSGA13	
cg25358294	5	131332149	ACSL6	
cg03063413	15	25965140	ATP10A	
cg14730017	9	96224366	FAM120A	
cg21452109	2	100878303	NA	
cg17944300	7	68899546	NA	eosinophilia
cg19599611	15	35148637	AQR	aging; atopy; eosinophilia; perinatally-acquired HIV ancestry
cg09602644	8	101502375	NA	
cg13252882	2	10135261	GRHL1	
cg02235918	6	72043561	NA	asthma; ancestry
cg03230255	11	15142113	INSC	dimethyl fumarate treatment in multiple sclerosis patients
cg07526904	7	3794264	SDK1	atopy
cg11292644	17	27284543	SEZ6	aging
cg27221998	3	186002153	DGKG	alcohol withdrawal recovery

cg10040196	14	100259352	EML1	
cg07891716	1	65744567	DNAJC6	
cg21640561	4	99416607	TSPAN5	
cg08386859	12	48359692	TMEM106C	
cg23858831	11	18620693	SPTY2D1-AS1	
cg20885688	5	74956618	ANKDD1B	
cg21625800	4	154678849	RNF175	
cg23331608	6	114196814	NA	
cg13531322	16	21142237	DNAH3	
cg06245989	11	16828408	PLEKHA7	thyroid lesion; smoking
cg09243552	4	148639367	NA	
cg07248935	6	90643780	BACH2	
cg03195622	21	32683087	TIAM1	
cg24447116	1	46126233	GPBP1L1	
cg10111648	9	134065507	NUP214	
cg22995183	16	14293184	MKL2	Smoking; Crohn's disease
cg14392653	9	127114252	NEK6	
				schizophrenia; gestational age; maternal hypertensive disorders in pregnancy; Crohn's disease; B Acute Lymphoblastic Leukemia with t(12; 21)(p13.2; q22.1); ETV6-RUNX1; Creutzfeldt-Jakob disease; multiple sclerosis
cg09007354	1	54100163	GLIS1	
cg26540230	15	85147051	ZSCAN2	
cg07258300	2	127963590	CYP27C1	
cg09221482	6	161557754	AGPAT4	Crohn's disease
cg13711762	10	76598375	KAT6B	
cg02019746	12	53254214	NA	
cg13165240	17	3715743	C17orf85	aggressive behavior; Aggressive behaviour; air pollution (NO2); C-reactive protein
cg06968354	16	49860902	ZNF423	Hyperdiploid B Acute Lymphoblastic Leukemia
cg09527658	12	54610034	NA	breast cancer
cg11016299	1	113256701	PPM1J	myalgic encephalomyelitis/chronic fatigue syndrome; Gulf War Illness
cg07579663	9	90292589	DAPK1	
cg06013057	9	38683518	NA	
cg20325814	1	151611101	SNX27	
cg16300310	12	133381504	GOLGA3	
cg27279968	3	47164794	SETD2	
cg08343295	4	41162279	APBB2	
cg03673225	13	99096762	FARP1	
cg09442355	5	172381049	NA	
cg13277131	12	1650978	NA	
cg06674440	1	108152369	VAV3	
cg09225336	16	65635750	NA	Werner syndrome

cg18265326	16	65635738	NA	Werner syndrome
cg19420069	16	65635834	NA	Werner syndrome
cg03112269	20	50349428	ATP9A	
cg25449870	7	7165860	NA	
cg20420249	1	172378938	DNM3	down syndrome
cg25570328	2	108903952	SULT1C2	smoking; body mass index (BMI); estimated glomerular filtration rate (eGFR); preeclampsia; maternal depression; multiple sclerosis
cg00813162	14	69443362	ACTN1	Crohn's disease; multiple sclerosis
cg07877229	7	142554307	EPHB6	eosinophilia; atopy
cg21566773	10	72034595	NPFFR1	Crohn's disease
cg09114605	2	196478714	NA	sarcopenic
cg20361768	3	156819083	LINC00880	ancestry; alcohol withdrawal recovery; maternal PM10 exposure in third gestational week
cg02117271	5	10618513	ANKRD33B	eosinophilia; down syndrome; air pollution (NO2)
cg03646542	5	172076155	NEURL1B	smoking
cg05673431	17	25871504	KSR1	alcohol withdrawal recovery
cg27529588	13	20975121	NA	eosinophilia; atopy; smoking; ancestry
cg26376393	15	31266654	MTMR10	
cg17635409	16	66836220	CCDC79	
cg07226581	9	37859354	DCAF10	
cg01995393	19	8563628	PRAM1	alcohol withdrawal recovery
cg09133793	20	10482949	SLX4IP	Gulf War Illness
cg13125822	10	121061302	GRK5	Crohn's disease
cg17922226	7	143013614	CLCN1	Crohn's disease; right insular surface area
cg02867043	2	60722786	BCL11A	
cg20817752	11	64030025	PLCB3	
cg11262246	13	96406302	DNAJC3	acetochlor; fractional exhaled nitric oxide
cg12082522	15	90380255	AP3S2	fractional exhaled nitric oxide
cg23007087	15	90380258	AP3S2	gestational age; fractional exhaled nitric oxide
cg23010507	5	1555887	NA	colorectal cancer; cell-specific characterization of the placental methylome; breast cancer; Kashin-Beck disease (KBD); multiple sclerosis
cg13005202	5	1555844	NA	colorectal cancer; cell-specific characterization of the placental methylome; child abuse; type 2 diabetes (T2D); maternal perfluoroalkyl substance exposure; multiple sclerosis
cg13573513	12	14996143	ART4	gestational age; air pollution (NO2); perinatally-acquired HIV; maternal depression; down syndrome
cg23064873	8	37457573	NA	Crohn's disease; fractional exhaled nitric oxide

cg16143123	1	52545864	BTF3L4	soluble tumor necrosis factor receptor 2
cg09479650	16	85578516	NA	(sTNFR2) levels in plasma; smoking; malignant pleural mesothelioma; preeclampsia
cg16500036	7	68983906	NA	Crohn's disease; gestational diabetes mellitus
cg21891812	10	65463235	NA	
cg03315921	22	18243630	BID	Coagulation factor VIII
cg01903241	7	158049946	PTPRN2	
cg15049460	3	24720314	NA	
cg02453588	9	110331783	NA	smoking
cg27363347	2	129151868	NA	eosinophilia
cg15357639	3	9790443	OGG1	
cg02792220	20	21196343	KIZ	
cg09697104	18	55212722	FECH	
cg13055436	3	114781015	ZBTB20	
cg12568458	16	19589790	C16orf62	fractional exhaled nitric oxide
cg13518537	8	28618150	NA	aging; systemic lupus erythematosus (SLE)
cg13624320	5	134734938	H2AFY	prenatal arsenic exposure
cg27456487	17	56349062	MPO	eosinophilia; air pollution (NO2); multiple sclerosis
cg07791286	11	72927001	NA	
cg16530978	2	144414276	ARHGAP15	
cg05638011	11	73691625	UCP2	
cg06277481	19	8408146	KANK3	
cg00968301	13	43965336	ENOX1	
cg10079576	6	135328150	HBS1L	
cg00442390	6	56584334	RNU6-71P; DST	
cg01561259	17	78560781	RPTOR	smoking; ancestry; air pollution (NO2)
cg22914245	2	20377884	NA	
cg04417471	19	54619164	PRPF31; TFPT	
cg25563198	6	35696726	FKBP5; LOC285847	Crohn's disease
cg07222912	6	11584784	NA	
cg00971396	3	184081400	POLR2H	smoking
cg00996690	12	50451095	ACCN2	high saturated fatty acids diet; hepatitis B virus (HBV)-related liver disease progression
cg03004126	16	11325588	NA	psoriasis; hepatitis B virus (HBV)-related liver disease progression
cg05870818	19	7765019	FCER2	gestational diabetes mellitus
cg10858644	22	37345239	NA	parenting stress
cg15402399	13	46189899	FAM194B	hepatitis B virus (HBV)-related liver disease progression
cg15981626	3	71355303	FOXP1	Gulf War Illness; myalgic encephalomyelitis/chronic fatigue syndrome
cg18991242	7	154722142	LOC100132707	placental microbes

cg19056772	17	7341616	FGF11	prostate cancer; atopy; allergic rhinitis; primary Sj 枚 gren Syndrome (pSS)
cg19888099	22	23274312	NA	end-stage kidney disease attributed to diabetic kidney disease
cg01315621	2	241065850	NA	
cg05248695	9	127115853	PSMB7; LOC100129034	
cg17595653	11	95550929	CEP57	
cg12616114	6	143130570	HIVEP2	
cg05449373	11	118095405	AMICA1	
cg11420771	1	85913350	DDAH1	
cg22146350	16	34982739	FLJ26245	
cg05116656	5	94417892	MCTP1	
cg23250906	1	202548017	PPP1R12B	
cg08378275	16	48282550	MIR548AE2; LONP2	
cg09894169	1	61423884	NFIA-AS2	
cg10272433	7	100732423	TRIM56	
cg03811828	3	140834386	SPSB4	
cg05809135	11	8987837	TMEM9B; TMEM9B- AS1	
cg19539732	8	23294732	ENTPD4	
cg10471451	2	27546430	MPV17	
cg12664184	8	94706496	LINC00535	

Supplementary Table 2. The relationship between 70 prognosis-associated DMPs and the expression levels of their nearby or targeted genes

Probe	CHR	BP	UCSC_RefGene	Related_Gene	Cor	P_value
cg19526450	5	142254301	ARHGAP26	ARHGAP26	-0.490	4.810E-25
cg26869211	17	58309224	USP32	USP32	-0.411	2.499E-17
cg00716819	10	71882625	AIFM2	AIFM2	0.394	5.610E-16
cg13518537	8	28618150	EXTL3	EXTL3	-0.371	3.066E-14
cg02235918	6	72043561	OGFRL1;LINC00472	OGFRL1	-0.328	2.867E-11
cg20005350	5	111478628	EPB41L4A	EPB41L4A-AS1	0.319	1.104E-10
cg12992827	3	101901234	ZPLD1	NFKBIZ	-0.319	1.137E-10
cg09663430	22	18251942	BID	BID	-0.291	4.690E-09
cg11237636	10	126380541	FAM53B	FAM53B	-0.279	2.087E-08
cg17635409	16	66836220	TERB1	NAE1	0.275	3.397E-08
cg27221998	3	186002153	DGKG	DGKG	-0.262	1.425E-07
cg17953136	2	20232577	LAPTM4A	LAPTM4A	-0.256	2.841E-07
cg13673960	4	1742301	TACC3	TACC3	-0.205	4.619E-05
cg12568458	16	19589790	VPS35L	VPS35L	0.190	1.523E-04
cg21371012	8	119269219	SAMD12	EXT1	-0.177	4.372E-04
cg00013899	1	64992433	CACHD1	JAK1	-0.174	5.676E-04
cg15981626	3	71355303	FOXP1	FOXP1	-0.171	6.712E-04
cg04893281	10	97732939	ENTPD1-AS1	ENTPD1-AS1	-0.169	7.823E-04
cg22416486	15	79704442	TMED3	TMED3	0.166	9.556E-04
cg05673431	17	25871504	KSR1	KSR1	0.165	1.042E-03
cg10272433	7	100732423	TRIM56	TRIM56	-0.161	1.391E-03
cg08960917	9	127114588	NEK6	NEK6	-0.160	1.505E-03
cg25114611	6	35696870	FKBP5;LOC285847	FKBP5	-0.159	1.646E-03
cg27430693	12	94208276	CRADD	CRADD	-0.158	1.735E-03
cg09481056	16	2339260	ABCA3	ABCA3	0.155	2.057E-03
cg04944536	12	116756890	MED13L	MED13L	-0.151	5.223E-03
cg04213647	13	99499944	DOCK9	DOCK9	0.135	7.361E-03
cg09007354	1	54100163	GLIS1	NDC1	0.132	8.751E-03
cg06258764	10	73510169	CDH23	CDH23	-0.128	1.141E-02
cg02453046	21	17210173	USP25	USP25	-0.126	1.282E-02
cg12828354	5	149466715	CSF1R	CSF1R	-0.123	1.494E-02
cg25563198	6	35696726	FKBP5;LOC285847	FKBP5	-0.115	2.300E-02
cg16500036	7	68983906		AUTS2	0.110	2.977E-02
cg22282161	7	21590890	DNAH11	SP4	0.110	3.019E-02
cg14932313	14	25043420	CTSG	CTSG	-0.112	3.911E-02
cg13711762	10	76598375	KAT6B	KAT6B	0.101	4.691E-02
cg24348980	1	232073393	DISC1-IT1;DISC1	DISC1	-0.099	4.937E-02
cg23064873	8	37457573		ZNF703	-0.088	8.108E-02

cg19782190	14	103487004	CDC42BPB	CDC42BPB	-0.084	9.558E-02
cg27380880	12	65022110	RASSF3	RASSF3	-0.078	1.213E-01
cg13125822	10	121061302	GRK5	GRK5	0.073	1.495E-01
cg04036920	11	33562503	C11orf41	C11orf41	-0.077	1.567E-01
cg17633019	7	143015959	CLCN1	CASP2	-0.070	1.689E-01
cg08538581	1	162500634	UHMK1	UHMK1	0.066	1.907E-01
cg10985150	6	150989765	PLEKHG1	MTHFD1L	0.061	2.320E-01
cg10079576	6	135328150	HBS1L	HBS1L	-0.060	2.345E-01
cg09894169	1	61423884	NFIA-AS2;NFIA	NFIA	0.054	2.851E-01
cg02453588	9	110331783	KLF4	KLF4	0.052	3.046E-01
cg08421448	16	31106703	VKORC1	VKORC1	0.044	3.812E-01
cg00442390	6	56584334	DST	DST	-0.038	4.520E-01
cg01561259	17	78560781	RPTOR	RPTOR	0.035	4.937E-01
cg11058932	7	130372167	TSGA13	COPG2	0.033	5.161E-01
cg12234768	2	88862824	EIF2AK3	EIF2AK3	0.032	5.231E-01
cg15685198	2	135163836	MGAT5	MGAT5	-0.032	5.277E-01
cg01068906	16	50745944	NOD2	NOD2	-0.025	6.212E-01
cg22995183	16	14293184	MRTFB	MRTFB	0.024	6.316E-01
cg13619623	7	33637324	BBS9	BBS9	0.024	6.404E-01
cg09479650	16	85578516	GSE1	GSE1	-0.023	6.539E-01
cg13165240	17	3715743	C17orf85	C17orf85	0.020	7.173E-01
cg19599611	15	35148637	AQR	AQR	-0.017	7.417E-01
cg18600016	8	95772595	DPY19L4	DPY19L4	-0.013	8.031E-01
cg24246360	6	82954226	IBTK	IBTK	-0.012	8.135E-01
cg07877229	7	142554307	EPHB6	EPHB6	0.011	8.241E-01
cg00748072	2	174862824		SP3	-0.011	8.395E-01
cg05773425	1	16644480	FBXO42	FBXO42	-0.009	8.597E-01
cg21163665	12	124657078	ZNF664-FAM101A	ZNF664	0.006	9.042E-01
cg05459163	14	92411904	FBLN5	FBLN5	-0.006	9.120E-01
cg27554156	12	13248725	GSG1	GSG1	-0.003	9.515E-01
cg06872019	13	31588778	LINC01066			
cg21223135	6	149320810	UST			

The correlation efficient and P values were calculated using a two-sided Pearson's correlation coefficient assays.

Supplementary Table 3. The primer information used in the genotyping of Fkbp5 knockout mice

	Primers1	Primers2
F1	5'- CTTTGCTGTTTAGGAAGTCC AGCA-3'	5'- CTTTGCTGTTTAGGAAGTCCA GCA-3'
R1/R2	5'- CCAGAGATGACTGTCACTG ATGC-3'	5'- GGATACAAAGGCCACAAGGAC TA-3'
Product size	252bp	410bp