

Supplementary Table S1: Significantly differentially methylated CpG sites selected according to their contribution to the PCA.

Cpg sites	Position	Relation	Gene	Island position	Location
cg20707527	8 q23.1	Genetic	ZFPM2	S_Shore	
cg20381372	19 q13.12	Intergenic	LOC100134317	S_Shelf	TSS1500
cg20022036	6 p21.32	Genetic	HLA-DRB1	N_shelf	Body
cg15084585	8 q23.1	Genetic	ZFPM2	S_Shore	
cg23024343	7 q22.3	Genetic	COG5	N_Shelf	Body
cg20485733	17 p13.3	Genetic	RAP1GAP2	Open Sea	Body
cg20239921	7 q 11.23	Genetic (Pseudogene)	DTX2P1- UPK3BP1- PMS2P11	Open Sea	Body
cg07040661	11 p15.5	Genetic	MUC2	N_Shelf	Body
cg25458175	19 q13.43	Genetic	ZBTB45	Island	Body
cg07180897	6 p21.32	Genetic	HLA-DQB2	N_Shore	Body
cg08720517	5 q 31.2	Genetic	PROB1	Island	1 st Exon
cg14073541	9 q 33.3	Genetic	DENND1A	Open Sea	Body
cg07458466	12 p 12.2	Genetic	PLCZ1	Open sea	Body
cg09642739	8 p 11.21	Genetic	HOOK3	Open Sea	Body
cg22949274	11 q 23.1	Genetic	SDHD	S_Shelf	Body
cg01437515	1 p 36.33	Genetic	TNFRSF4		
cg24840300	19 p13.3	Genetic	PLPR3	Island	3'UTR
cg25828445	12 p13.31	Intergenic (Pseudogene)	NIFKP3	S_Shore	
cg11445109	10 q26.3	Genetic	CYP2E1	S_Shore	Body
cg19469447	10 q26.3	Genetic	CYP2E1	Island	Body
cg17172308	6 q27	Intergenic	FRMD1	S_Shelf	
cg05473257	10 q26.3	Genetic	CYP2E1	Island	Body
cg14906510	12 p 13.31	Genetic	NIFKP3	Island	
cg05194426	10 q26.3	Genetic	CYP2E1	S_Shore	Body
cg23400446	10 q26.3	Genetic	CYP2E1	Island	Body
cg26805839	9p24.2	Genetic	SLC1A1	Open Sea	Body

Supplementary Table S2: Significantly differentially methylated CpG sites in the in-depth analysis of identified genes in the double PCA selection.

Gene	Cpg	P-value
ZBTB45e	cg18521743	0.0450
	cg21517584	0.0079
	cg10598434	0.0249
DENND1A	cg14073541	0.0392
RAP1GAP2	cg20485733	0.0443
	cg15586931	0.0415
	cg21022776	0.0369
MUC2	cg08804537	0.0272
	cg26740937	0.0490
	cg27483767	0.0481
	cg11415512	0.0291
Zona 5' MUC2	cg05285917	0.0278
Zona 3' MUC2	cg12306296	0.0244
CYP2E1	cg13315147	0.0071
	cg10862468	0.0375
	cg25330361	0.0489
	cg24530264	0.0390
	cg18984983	0.0053
HLA-DRB1	cg19575208	0.0051
	cg10765922	0.0040
	cg26036029	0.0300
	cg24147543	<0.001
ZFPM2	cg21425607	0.0138
	cg27281791	0.0197
	cg00112309	0.0484
SLC1A1	cg02464768	0.0037
	cg16545428	0.0419
DTX2P1-UPK3BP1-PMS2P11	cg12123692	0.0264
COG5	cg24382300	0.0122
	cg24648061	0.0404
	cg06593906	0.0360
	cg22438280	0.0203
HLA-DQB2	cg20645912	0.0137
	cg03638120	0.0104
	cg18609891	0.0265
PLCZ1	cg25473831	0.0183
	cg21522539	0.0448
	cg24806623	0.0466
HOOK3	cg17145652	0.0425
	cg00741600	0.0234

	cg02204844	0.0204
	cg11371500	0.0204
FRDM1	cg03002835	0.0085
DTX2P1-UPK3BP1-PMS2P11 flank	cg16669468	0.0024

Supplementary Table S3: Gene ontology annotation of the 26 differentially methylated CpG sites.

Gene Ontology accession (term)	CpG site	Gene
CELULAR COMPONENTS		
GO:0032588 (trans-Golgi network membrane)	cg23024343	component of oligomeric golgi complex 5(COG5)
	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)
	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
GO:0042613 (MHC class II protein complex)	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)
GO:0030669 (Clathrin-coated endocytic vesicle membrane)	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)
	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
GO:0042611 (MHC class protein complex)	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)
GO:0071556 (Integral component of luminal side of endoplasmic reticulum membrane)	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)
	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
GO:0098553 (luminal side of endoplasmic reticulum membrane)	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)
	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
GO:0031227 (intrinsic component of endoplasmic reticulum membrane)	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)
	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
GO:0098576 (luminal side of membrane)	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)
	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
GO:0030662 (coated vesicle membrane)	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)
	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
MOLECULAR FUNCTION		
GO:0032395	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)

(MHC class II receptor activity)	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
GO:0033229 (cysteine transmembrane transporter activity)	cg26805839	solute carrier family 1 member 1 (SLC1A1)
GO:0140010 (D-aspartate transmembrane transporter activity)	cg26805839	solute carrier family 1 member 1 (SLC1A1)
GO:0018601 (4-nitrophenol 2-monooxygenase activity)	cg05473257	Cytochrome P450 2E1(CYP2E1)
	cg05194426	
	cg23400446	
	cg11445109	
	cg19469447	
GO:0032266 (phosphatidylinositol-3-phosphate binding)	cg07458466	phospholipase C, zeta 1 (PLCZ1)
GO:0042943 (D-amino acid transmembrane transporter activity)	cg26805839	solute carrier family 1 member 1 (SLC1A1)
GO:0000104 (succinate dehydrogenase activity)	cg22949274	Succinate dehydrogenase [ubiquinone] (SHDH)
GO:0140375 (immune receptor activity)	cg20022036	major histocompatibility complex, class II, DR beta 1 (HLA-DRB1)
	cg07180897	major histocompatibility complex, class II, DQ beta 2 (HLA-DQB2)
GO:0020037 (heme binding)	cg22949274	Succinate dehydrogenase [ubiquinone] (SHDH)
GO:0005314 (high-affinity glutamate transmembrane transporter activity)	cg26805839	solute carrier family 1 member 1 (SLC1A1)
BIOLOGICAL PROCESS		
GO:0060470 (positive regulation of cytosolic calcium ion concentration involved in egg activation)	cg07458466	phospholipase C, zeta 1 (PLCZ1)
GO:1903712 (cysteine transmembrane transport)	cg26805839	solute carrier family 1 member 1 (SLC1A1)

GO:0018885 (carbon tetrachloride metabolic process)	cg05473257	Cytochrome P450 2E1(CYP2E1)
	cg05194426	
	cg23400446	
	cg11445109	
	cg19469447	
GO:0018910 (benzene metabolic process)	cg05473257	Cytochrome P450 2E1(CYP2E1)
	cg05194426	
	cg23400446	
	cg11445109	
	cg19469447	
GO:0018960 (4-nitrophenol metabolic process)	cg05473257	Cytochrome P450 2E1(CYP2E1)
	cg05194426	
	cg23400446	
	cg11445109	
	cg19469447	
GO:0048219 (inter-Golgi cisterna vesicle-mediated transport)	cg23024343	Golgi complex subunit 5 (COG5)
GO:0042883 (cysteine transport)	cg26805839	solute carrier family 1 member 1 (SL1CA1)
GO:0042197 (halogenated hydrocarbon metabolic process)	cg05473257	Cytochrome P450 2E1(CYP2E1)
	cg05194426	
	cg23400446	
	cg11445109	
	cg19469447	
GO:0016098 (monoterpenoid metabolic process)	cg05473257	Cytochrome P450 2E1(CYP2E1)
	cg05194426	
	cg23400446	
	cg11445109	
	cg19469447	

GO:0006121 (mitochondrial electron transport, succinate to ubiquinone)	cg22949274	Succinate dehydrogenase [ubiquinone] (SHDH)
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Supplementary Figure S1. Top 10 Gene Ontology (GO) terms enriched by differentially methylated genes in stable MHO and unstable MHO groups. Enriched GO terms were categorized into (a) biological processes, (b) molecular function and (c) cellular components. Data are presented as enriched scores expressed as $-\log_{10}$ (p value).

