Supplement I

Table S1. Association of neutrophil proportion with DNA methylation of the recent blood samples of 34 additional individuals from the NTR biobank

Locus	Variance explained	p-value of effect
IL10	27.9 %	$8.0*10^{-08}$
IGF2R	1.2 %	0.312
LEP	1.8 %	$1.0*10^{-04}$
CRH	0.0 %	0.993
IGF2	0.6 %	0.378
INSIGF	0.1 %	0.677
KCNQ1OT1	0.0 %	0.808
APOC1	0.1 %	0.763

Table S2. Characteristics of 30 individuals, selected from the NTR biobank

Male, no. (%)	12	(40 %)
Female, no. (%)	18	(60 %)
Smoker, no. (%)	3	(10 %)
Ex-smoker, no. (%)	15	(50 %)
Non-smoker, no. (%)	12	(40 %)
Age at biobanking, mean (SD)	48	(16)
Waist circumference in cm, mean (SD)	98	(22)
LDL-cholesterol (in mmol/L) , mean (SD)	2.47	(1.63)
HDL-cholesterol (in mmol/L) , mean (SD)	1.51	(0.94)
Glucose (in mmol/L) , mean (SD)	9.10	(4.83)

Table S3. Age and longitudinal sampling of 34 individuals from the NTR biobank

Age at first sampling (blood)	Years to first follow-up (buccal swab)	Years to second follow-up (blood and buccal swab)
62	6	13
62	6	13
60	9	12
54	6	14
52	6	13
52	6	13
48	6	13
48	6	13
46	10	12
46	10	12
45	10	12
45	10	12
43	6	13
43	6	12
42	6	11
41	6	13
41	10	12
41	6	12
41	10	12
39	6	11
39	9	12
36	10	12
36	10	14
36	10	12
34	9	12
21	13	15
19	10	16
17	15	17
17	14	16
16	11	16
16	13	16
14	17	19
14	16	18
14	15	19

Table S4. Primers used in bisulfite PCR

Locus	Forward primer[1]	Reverse primer[2]
IL10	TGATTGGTTGAATATGAATTTTTGTAT	CACCCCCTCATTTTTACTTAAAAA
NR3C1	GATTTGGTTTTTTTGGGG	TCCCTTCCCTAAAACCT
TNF	GGGTATTTTTGATGTTTGTGTGTT	CAATACTCATAATATCCTTTCCAAAAAA
IGF2R	AGGTAGAAAAAGGTTTTGGAAG	CAAATCTTAAAAACTAACTAAAAACC
GRB10	GGAATTTTAGGATTAAATTTATGTGA	AACTTCCAAAAAAAAACCTCTCC
LEP	GTTTTTGGAGGGATATTAAGGATTT	CTACCAAAAAAAAACCAACAAAAAAA
CRH	TGGTTGTTGTTTTTTTGGTAGG	AATTTCTCCACTCCAAAACCTAAA
ABCA1	ATTTTATTGGTGTTTTTGGTTGT	ATCAAAACCTATACTCTCCCTCCTC
IGF2	TGGATAGGAGATTGAGGAGAAA	AAACCCCAACAAAAACCACT
INSIGF	GTTTTGAGGAAGAGGTGTTGA	ACCTAAAATCCAACCACCCTAA
KCNQ1OT1	TTTGGTAGGATTTTGTTGAGGAGTTTT	CTCACACCCAACCAATACCTCATAC
MEG3	TTTTTTTTAATAGTATTTTGATTTTTG	AAATAATCCCCACACACATACC
FTO	GTTTGTAATTTTAGTATTTTGGGAGGT	TTTATTTCCATTTATCCATTCTCAAA
APOC1	GGAGGAGGGAGATTAATATTAATTTGT	ACCCCAAACCTATAACCACCTT
GNASAS	GTAATTTGTGGTATGAGGAAGAGTGA	TAAATAACCCAACTAAATCCCAACA
GNAS A/B	ATGATTTAATTAAGGTTTTAGGAAAGG	TAAAAATACAAAACCTCCCCTACTC
10-mer tag	AGGAAGAGAG + primer	
T7 tag		CAGTAATACGACTCACTATAGGGAGAAGGCT + primer

1. Forward primer, an additional tag is added for Sequenom Epityper PCRs which is denoted below
2. Reverse primer, an additional tag is added for Sequenom Epityper PCRs which is denoted below

Table S5. CpG-sites per fragment of the loci that were analyzed for variation

Locus	CpG-sites* analyzed
IL10	1, 2&3, 4
NR3C1	1&2, 4, 7&8, 9, 10&11, 12&13, 14, 15&16, 17-20, 31, 33&34
TNF	1-3, 5, 6, 9, 10, 11
IGF2R	4&5, 8-10, 11-13, 20&21
GRB10	1&2, 4-6, 7, 8, 17, 18-21, 22&23, 24, 25
LEP	1, 8, 16%17, 19-21, 22, 25, 27
CRH	1, 2, 5, 9, 10
ABCA1	1, 3&4, 6-9, 15&16, 17&18, 19-21, 24, 25
IGF2	3, 4, 6&7, 8
INSIGF	2, 4, 5, 6
KCNQ1OT1	1, 6, 8&9, 10-12, 15, 16, 17&18, 20, 21, 25
MEG3	2, 3, 4, 8&9, 10&11
FTO	2&3, 7, 8&9, 10&11, 14, 17, 19
APOC1	1, 2, 3, 4, 10, 11
GNASAS	1&2, 3&4, 6, 7, 8&9, 10-12, 13&14, 15, 17-19
GNAS A/B	1, 3&4, 7, 8, 13-15, 16-19

* CpG-site number is counted from the forward primer onward

Table S6. CpG-sites per fragment of the loci that were analyzed for stability

Locus	CpG-sites* analyzed
IL10	1, 2&3, 4
IGF2R	4&5, 8-10, 11-13, 20&21, 22†
LEP	1, 8, 16&17, 19-21, 22†, 25, 27
CRH	1†, 2, 5, 9
IGF2	4, 6&7, 8
INSIGF	2, 4, 5, 6
KCNQ1OT1	1, 6, 10-12, 15, 16, 17&18, 20, 21, 25
APOC1	1, 2, 3, 4, 10, 11

* CpG-site number is counted from the forward primer onward

† CpG-site measurement met the quality criteria only in the recent blood samples

Table S7. All CpG-units of the 16 loci

Locus_CpG-unit*	CpG-sites*	Reason for removal prior to quality control
*IL10*_01	CpG_1	
*IL10*_02	CpG_2&3	
*IL10*_03	CpG_4	
*NR3C1*_01	CpG_1&2	
*NR3C1*_02	CpG_3	
*NR3C1*_03	CpG_4	
*NR3C1*_04	CpG_5&6	
*NR3C1*_05	CpG_7&8	
*NR3C1*_06	CpG_9	
*NR3C1*_07	CpG_10&11	
*NR3C1*_08	CpG_12&13	
*NR3C1*_09	CpG_14	
*NR3C1*_10	CpG_15&16	
*NR3C1*_11	CpG_17-20	
*NR3C1*_12	CpG_21	Mass overlap with unit 14
*NR3C1*_13	CpG_22-28	
*NR3C1*_14	CpG_29	Mass overlap with unit 12
*NR3C1*_15	CpG_30	
*NR3C1*_16	CpG_31	
*NR3C1*_17	CpG_32	
*NR3C1*_18	CpG_33&34	
*NR3C1*_19	CpG_35-41	High Mass
*NR3C1*_20	CpG_42	rs5871844 and rs34027900
*TNF*_01	CpG_1-3	
*TNF*_02	CpG_4	
*TNF*_03	CpG_5	
*TNF*_04	CpG_6	
*TNF*_05	CpG_7&8	
*TNF*_06	CpG_9	
*TNF*_07	CpG_10	
*TNF*_08	CpG_11	
*IGF2R*_01	CpG_1	Mass overlap with unit 8
*IGF2R*_02	CpG_2	Mass overlap with unit 3
*IGF2R*_03	CpG_3	Mass overlap with unit 2
*IGF2R*_04	CpG_4&5	
*IGF2R*_05	CpG_6&7	Mass overlap with unit 11
*IGF2R*_06	CpG_8-10	
*IGF2R*_07	CpG_11-13	
*IGF2R*_08	CpG_14	Mass overlap with unit 1
*IGF2R*_09	CpG_15&16	Mass overlap with unit 10 and rs677882 and rs8191722
*IGF2R*_10	CpG_17	Mass overlap with unit 9
*IGF2R*_11	CpG_18&19	Mass overlap with unit 5 and rs8191721 and rs8191720
*IGF2R*_12	CpG_20&21	
*IGF2R*_13	CpG_22	

Table S7. (Continued A): All CpG-units of the 16 loci

Locus_CpG-unit*	CpG-sites*	Reason for removal prior to quality control
*GRB10*_01	CpG_1&2	
*GRB10*_02	CpG_3	Mass overlap with unit 9
*GRB10*_03	CpG_4-6	
*GRB10*_04	CpG_7	
*GRB10*_05	CpG_8	
*GRB10*_06	CpG_9&10	Mass overlap with unit 8
*GRB10*_07	CpG_11	Low mass
*GRB10*_08	CpG_12	Mass overlap with unit 6
*GRB10*_09	CpG_13	Mass overlap with unit 2
*GRB10*_10	CpG_14&15	
*GRB10*_11	CpG_16	
*GRB10*_12	CpG_17	
*GRB10*_13	CpG_18-21	
*GRB10*_14	CpG_22&23	
*GRB10*_15	CpG_24	
*GRB10*_16	CpG_25	
*LEP*_01	CpG_1	
*LEP*_02	CpG_2-7	High Mass and rs791620
*LEP*_03	CpG_8	
*LEP*_04	CpG_9&10	Mass overlap with unit 9
*LEP*_05	CpG_11	Mass overlap with units 12 and 6
*LEP*_06	CpG_12&13	Mass overlap with units 5 and 12
*LEP*_07	CpG_14&15	Mass overlap with unit 14
*LEP*_08	CpG_16&17	
*LEP*_09	CpG_18	Mass overlap with unit 4
*LEP*_10	CpG_19-21	
*LEP*_11	CpG_22	
*LEP*_12	CpG_23&24	Mass overlap with units 5 and 6
*LEP*_13	CpG_25	
*LEP*_14	CpG_26	Mass overlap with unit 7
*LEP*_15	CpG_27	
*LEP*_16	CpG_28	
*LEP*_17	CpG_29	rs2167270
*LEP*_18	CpG_30-32	High Mass
*CRH*_01	CpG_1	
*CRH*_02	CpG_2	
*CRH*_03	CpG_3	
*CRH*_04	CpG_4	
*CRH*_05	CpG_5	
*CRH*_06	CpG_6	Mass overlap with unit 7
*CRH*_07	CpG_7	Mass overlap with unit 6
*CRH*_08	CpG_8	
*CRH*_09	CpG_9	
*CRH*_10	CpG_10	

Table S7. (Continued B): All CpG-units of the 16 loci

Locus_CpG-unit*	CpG-sites*	Reason for removal prior to quality control
*ABCA1*_01	CpG_1	
*ABCA1*_02	CpG_2	
*ABCA1*_03	CpG_3&4	
*ABCA1*_04	CpG_5	
*ABCA1*_05	CpG_6-9	
*ABCA1*_06	CpG_10-13	rs2246298
*ABCA1*_07	CpG_14	
*ABCA1*_08	CpG_15&16	
*ABCA1*_09	CpG_17&18	
*ABCA1*_10	CpG_19-21	
*ABCA1*_11	CpG_22&23	rs13306071
*ABCA1*_12	CpG_24	
*ABCA1*_13	CpG_25	
*ABCA1*_14	CpG_26&27	rs2740483
*IGF2*_01	CpG_1	rs3741208 and rs17883577
*IGF2*_02	CpG_2	rs3741209
*IGF2*_03	CpG_3	
*IGF2*_04	CpG_4	
*IGF2*_05	CpG_5	rs4930041
*IGF2*_06	CpG_6&7	
*IGF2*_07	CpG_8	
*INSIGF*_01	CpG_1	Low mass
*INSIGF*_02	CpG_2	
*INSIGF*_03	CpG_3	
*INSIGF*_04	CpG_4	
*INSIGF*_05	CpG_5	
*INSIGF*_06	CpG_6	
*KCNQ1OT1*_01	CpG_1	
*KCNQ1OT1*_02	CpG_2	
*KCNQ1OT1*_03	CpG_3-5	Mass overlap with unit 8
*KCNQ1OT1*_04	CpG_6	
*KCNQ1OT1*_05	CpG_7	Mass overlap with units 15 and 19
*KCNQ1OT1*_06	CpG_8&9	
*KCNQ1OT1*_07	CpG_10-12	
*KCNQ1OT1*_08	CpG_13&14	Mass overlap with unit 3
*KCNQ1OT1*_09	CpG_15	
*KCNQ1OT1*_10	CpG_16	
*KCNQ1OT1*_11	CpG_17&18	
*KCNQ1OT1*_12	CpG_19	
*KCNQ1OT1*_13	CpG_20	
*KCNQ1OT1*_14	CpG_21	
*KCNQ1OT1*_15	CpG_22	Mass overlap with units 5 and 19
*KCNQ1OT1*_16	CpG_23	rs7940500
*KCNQ1OT1*_17	CpG_24	rs379976
*KCNQ1OT1*_18	CpG_25	
*KCNQ1OT1*_19	CpG_26&27	Mass overlap with units 5 and 15

Table S7. (Continued C): All CpG-units of the 16 loci

Locus_CpG-unit*	CpG-sites*	Reason for removal prior to quality control
*MEG3*_01	CpG_1	
*MEG3*_02	CpG_2	
*MEG3*_03	CpG_3	
*MEG3*_04	CpG_4	
*MEG3*_05	CpG_5	Mass overlap with unit 6
*MEG3*_06	CpG_6	Mass overlap with unit 5
*MEG3*_07	CpG_7	
*MEG3*_08	CpG_8&9	
*MEG3*_09	CpG_10&11	
*MEG3*_10	CpG_12-14	High Mass
*FTO*_01	CpG_1	Mass overlap with Unit 5
*FTO*_02	CpG_2&3	
*FTO*_03	CpG_4	Low mass
*FTO*_04	CpG_5	
*FTO*_05	CpG_6	Mass overlap with Unit 1
*FTO*_06	CpG_7	
*FTO*_07	CpG_8&9	
*FTO*_08	CpG_10&11	
*FTO*_09	CpG_12	Mass overlap with Unit 17
*FTO*_10	CpG_13	
*FTO*_11	CpG_14	
*FTO*_12	CpG_15	
*FTO*_13	CpG_16	
*FTO*_14	CpG_17	
*FTO*_15	CpG_18	
*FTO*_16	CpG_19	
*FTO*_17	CpG_20	Mass overlap with Unit 9
*APOCI*_01	CpG_1	
*APOCI*_02	CpG_2	
*APOCI*_03	CpG_3	
*APOCI*_04	CpG_4	
*APOCI*_05	CpG_5&6	rs402204
*APOCI*_06	CpG_7-9	High Mass and rs5111
*APOCI*_07	CpG_10	
*APOCI*_08	CpG_11	
*GNASAS*_01	CpG_1&2	
*GNASAS*_02	CpG_3&4	
*GNASAS*_03	CpG_5	
*GNASAS*_04	CpG_6	
*GNASAS*_05	CpG_7	
*GNASAS*_06	CpG_8&9	
*GNASAS*_07	CpG_10-12	
*GNASAS*_08	CpG_13&14	
*GNASAS*_09	CpG_15	
*GNASAS*_10	CpG_16	rs45596642
*GNASAS*_11	CpG_17-19	

Table S7. (Continued D): All CpG-units of the 16 loci

Locus_CpG-unit*	CpG-sites*	Reason for removal prior to quality control
*GNAS A/B*_01	CpG_1	
*GNAS A/B*_02	CpG_2	Mass overlap with unit 4
*GNAS A/B*_03	CpG_3&4	
*GNAS A/B*_04	CpG_5&6	Mass overlap with unit 2
*GNAS A/B*_05	CpG_7	
*GNAS A/B*_06	CpG_8	
*GNAS A/B*_07	CpG_9&10	
*GNAS A/B*_08	CpG_11	Low mass
*GNAS A/B*_09	CpG_12	
*GNAS A/B*_10	CpG_13-15	
*GNAS A/B*_11	CpG_16-19	
Totals		
# of amplicons		16
total # units		191
# units outside detection range		9
# units with equal or overlapping mass		36
# units with potential SNP		12
Total # CpG-units removed		**87**

* CpG-unit and CpG-site numbers are counted from the forward primer onward

Table S8. Primers used in Chapter 6

Locus	Location NCBI36/hg18	Strand	Amplicon (bp)	Forward primer[1] 5'-3'	Reverse primer[2] 5'-3'
*H19*DMR	chr 11: 1975948-1976360	-	413	GGGTTTGGGAGAGTTTGTGAGGT	ATACCTACTACTCCCTACCTACCAAC
*IGF2*DMR2	chr11: 2111300-2111791	+	492	GGAAAGGGGTTTAGGATTTTTAT	AACCACTCCCATTATAAACCTTTAAT
*IGF2*DMR2 CTCF	chr11 2112023-2112312	+	290	TAGTAATGTTTAGTTGGAAGGGGAA	ACTACTTAACTCTAAAAACCCCTACCC
*IGF2*AS	chr11: 2117482-2117948	+	467	TTTTAGAGAATTTAGGGGTTTTATTT	CCATACAAATAAAATTTAAACTATATTTCC
*IGF2*AS CTCF	chr11: 2118126-2118422	-	297	GGTTGGAGGGTTTTAAAGTGG	AAAAAAACACTATAATTTTTACCAAATCAA
*IGF2*DMR0 upstr.	chr11: 2125961-2126065	-	105	GTTGTGTGTTTAGTGGTTTTTGTTG	AAAAAATTTACCTAAAAAAAACTTCCC
*IGF2*DMR	chr11: 2126035-2126372	-	338	TGGATAGGAGATTGAGGAGAAA	AAACCCCAACAAAAACCACT
*IGF2*DMR0 downstr.	chr11: 2127117-2127220	-	104	GATGAGGTTTTTTTATTTGTAGGGG	AAAACCAAAATCCTAACAACTACCC
INSIGF	chr11:2138912-2139216	-	305	GTTTTGAGGAAGAGGTGTTGA	ACCTAAAATCCAACCACCCTAA
LINES-1	X58075: 335–767	-	432	GTGTGAGGTGTTAGTGTGTTTTGTT	ATATCCCACACCTAACTCAAAAAAT
Additional	For Sequenom Epityper			AGGAAGAGAG + primer	CAGTAATACGACTCACTATAGGGAGAAGGCT + primer

1. Forward primer, an additional tag is added for Sequenom Epityper PCRs which is denoted below
2. Reverse primer, an additional tag is added for Sequenom Epityper PCRs which is denoted below

PCR was performed with the following cycling protocol: 15 minutes at 95°C, 4 rounds of 20 seconds at 95°C, 30 seconds at 65°C, 1 minute at 72°C; followed by 40 rounds, 20 seconds at 95°C, 30 seconds at 58°C and 1 minute at 72°C; ending with 3 minutes at 72°C.

Table S9. Details of CpG units measured in Chapter 6

Amplicon	CpGsite	Reason for exclusion	Success rate	Mean methylation[2]	SD[3]	Exp-Unexp[4]	P diff[5]
H19 DMR	CpG1	Mass-overlap with fragment CpG 16	95.0				
	CpG2		95.0	28.7	5.8	-0.2	0.91
	CpG3.4.5	Mass-overlap with fragment CpG 11	95.0				
	CpG6	low success rate	65.8				
	CpG7		89.2	32.2	3.2	-0.7	0.23
	CpG8		94.2	32.1	2.0	0.0	0.99
	CpG9.10		94.2	26.8	2.6	0.0	0.99
	CpG11	Mass-overlap with fragment CpG 3.4.5	95.8				
	CpG12	rs12292822	95.0	26.6	2.3	0.0	0.87
	CpG13		95.0	29.0	3.1	-0.2	0.61
	CpG14.15	rs12292818	95.0	31.5	2.5	0.0	0.98
	CpG16	Mass-overlap with fragment CpG 1	95.0				
	CpG17	rs35592994	94.2	29.0	2.4	-0.3	0.56
	CpG18.19		94.2	30.4	3.2	-0.2	0.71
	CpG20		95.0	30.0	3.0	-0.2	0.73
	CpG21	Low success rate	4.2				
	CpG22		86.7	34.0	8.0	-1.7	0.12
	CpG23	Low success rate	3.3				
	CpG24	Low success rate	65.0				
	CpG25		95.0	31.9	3.4	-0.7	0.21

Table S9. (Continued A) Details of CpG units measured in Chapter 6

Amplicon	CpGsite	Reason for exclusion[1]	Success rate	Mean methylation[2]	SD[3]	Exp-Unexp[4]	P diff[5]
IGF2 DMR2	CpG1	Low mass	0.0				
S.L.	CpG2.3	Mass-overlap with fragment CpG 9	65.8				
(DMR2)	CpG4		90.8	48.0	8.9	2.2	0.17
	CpG5.6		95.8	37.2	5.1	-0.3	0.88
	CpG7		94.2	49.8	9.3	0.0	0.96
	CpG8		96.7	56.7	8.2	0.5	0.74
	CpG9	Mass-overlap with fragment CpG 2.3	67.5				
	CpG10	Low mass	0.0				
	CpG11.12		95.0	47.7	5.6	-0.2	0.91
	CpG13		93.3	44.3	7.4	-0.3	0.83
	CpG14.15		96.7	55.5	8.2	0.7	0.68
	CpG16	Mass-overlap with fragment CpG 18 and 21	95.8				
	CpG17	Low success rate	3.3				
	CpG18	Mass-overlap with fragment CpG 16 and 21	95.8				
	CpG19	Low mass	0.0				
	CpG20		95.8	59.4	6.7	-1.0	0.43
	CpG21	Mass-overlap with fragment CpG 16 and 18	95.8				
	CpG22	High mass	0.0				
IGF2 DMR2 CTCF	CpG1		95.0	53.9	3.8	-1.7	0.040
(DMR2)	CpG2	Low success rate	70.8				
	CpG3		95.0	35.0	4.0	-1.4	0.056
	CpG4		95.0	63.5	2.4	-1.1	0.045

1. CpG containing fragments (e.g. 'CpG units'): excluded were fragments containing possible SNPs in CEU (by HAPMAP or 1000genomes), a measurement success rate below <75% or (partial) overlap with other units.
2. Mean methylation in %, based on the raw data.
3. the variation (in %) in the controls
4. The average within pair difference from a Linear Mixed Model, corrected for age and bisulfite batch.
5. The P value belonging to the within pair difference.

Table S9. (Continued B) Details of CpG units measured in Chapter 6

Amplicon	CpGsite	Reason for exclusion[1]	Success rate	Mean methylation[2]	SD[3]	Exp-Unexp[4]	P diff[5]
*IGF2*AS	CpG1.2.3.4	High mass	0.0				
(DMR1)	CpG5		97.5	8.3	2.8	0.7	0.16
	CpG6		85.0	16.4	3.0	3.1	0.070
	CpG7		96.7	5.6	2.6	-0.4	0.43
	CpG8.9.10		96.7	5.4	0.9	-0.2	0.40
	CpG11.12	High mass	0.0				
	CpG13.14.15.16	High mass	0.0				
	CpG17		95.0	5.2	1.5	0.3	0.25
	CpG18	Mass-overlap with fragment CpG 28	97.5				
	CpG19.20.21		97.5	2.5			
	CpG22	Low success rate	59.2				
	CpG23.24.25.26.27	High mass	0.0				
	CpG28	Mass-overlap with fragment CpG 18	97.5				
	CpG29		95.8	13.0	2.4	0.3	0.63
	CpG30		95.0	7.3	2.9	0.1	0.96
	CpG31.32.33		95.0	14.9	2.9	0.7	0.24
	CpG34.35.36.37		97.5	8.5	1.0	0.1	0.55
	CpG38	Low mass	0.0				
	CpG39.40		81.7	11.7	2.2	0.5	0.43
	CpG41		97.5	3.1	0.8	0.5	0.0030

Table S9. (Continued C) Details of CpG units measured in Chapter 6

Amplicon	CpGsite	Reason for exclusion[1]	Success rate	Mean methylation[2]	SD[3]	Exp-Unexp[4]	P diff[5]
*IGF2*AS CTCF	CpG1		98.3	2.5	1.7	0.2	0.61
(DMR1)	CpG2		98.3	0.6	0.6	0.0	0.99
	CpG3.4		92.5	14.9	2.9	0.5	0.42
	CpG5.6.7.8		98.3	4.1	0.9	0.1	0.37
	CpG9.10		95.8	5.1	0.8	0.3	0.11
	CpG11.12		97.5	5.7	1.7	0.6	0.11
	CpG13.14.15.16		97.5	6.9	2.5	0.8	0.063
	CpG17.18.19		91.7	6.4	3.4	0.9	0.20
	CpG20		95.8	1.6	0.8	0.4	0.0054
	CpG21	Low mass	0.0				
	CpG22		96.7	2.0	0.7	0.3	0.019
	CpG23.24		97.5	1.1	0.6	0.0	0.71
	CpG25.26.27	High mass	0.0				
	CpG28.29.30.31	High mass	0.0				
	CpG32		98.3	4.5	1.9	0.5	0.33

Table S9. (Continued D) Details of CpG units measured in Chapter 6

Amplicon	CpGsite	Reason for exclusion[1]	Success rate	Mean methylation[2]	SD[3]	Exp-Unexp[4]	P diff[5]
IGF2 DMR0 upstream	CpG1		94.2	46.6	5.4	-2.9	0.0056
(DMR0)	CpG2		92.5	51.6	7.3	-3.1	0.027
	CpG3		95.0	40.1	5.2	-2.7	0.0056
	CpG4		95.8	50.4	4.0	-1.4	0.049
	CpG5		91.7	32.6	4.3	-0.5	0.57
*IGF2*DMR0	CpG1	Low succes rate	56.7				
downstream	CpG2	Low succes rate	67.5				
(DMR0)	CpG3	Mass-overlap with fragment CpG 4	8.3				
	CpG4	Mass-overlap with fragment CpG 3	8.3				
	CpG5.6	Mass-overlap with fragment CpG 10	84.2				
	CpG7	Low succes rate	44.2				
	CpG8		77.5	82.7	5.7	-2.3	0.05
	CpG9		75.8	60.6	5.8	1.0	0.35
	CpG10	Mass-overlap with fragment CpG 5.6	82.5				
	CpG11	Low succes rate	25.0				
	CpG12.13	rs11601832, but not present in CEU	82.5	70.5	4.9	-3.6	8.5E-4
LINES-1	CpG_1		98.3	64.2	2.6	-1.8	5.8E-4
	CpG_2		98.3	60.0	1.4	-0.8	0.004
	CpG_3		98.3	71.6	2.1	-0.3	0.36
	CpG_4		96.7	36.9	4.6	-0.4	0.28
	CpG_5		97.5	35.3	1.3	-0.1	0.54
	CpG_6.7		98.3	69.4	2.0	0.1	0.13
	CpG_8.9		98.3	68.7	1.9	0.1	0.12
	CpG_10	Low mass					
	CpG_11.12		98.3	83.6	2.5	-0.4	0.31

Table S10. The genotyping results for the H19 LD block

SNP	Source[1]	Success rate[2]	included?[3]	MAF(obs.)	MAF CEU		HW Pval[4]	associations (Pubmed [uid]: type)
rs217727	both	100	YES	0.204	0.15	G:A	0.16	15885138: birthweight and newborn IGF2 levels
rs2839701	tagging	no design poss.						
rs2067051	both	94.2	No, below <95%	0.5	0.482	C:C	0.89	20639793: association with birth weight
rs2251375	both	98.3	YES	0.297	0.292	C:A	0.74	20639793: association with birth weight
rs10732516	candidate	98.3	covered by rs4929983	0.496	NA, 0.44 in Brazilians	T:C	1	In core binding motif 6th CTCF ICR
rs11042170	tagging	no design poss.						
rs2735971	tagging	no design poss.						
rs12417375	tagging	no design poss.						
rs4929983	tagging	100	YES	0.488	0.397	T:C	0.74	
rs4929984	both	98.3	covered by rs4929983	0.47	0.486	A:C	0.86	20639793: association with birth weight
rs12292757	tagging	98.3	YES	0.212	0.125	G:A	0.47	

1. Several SNPs were chosen from the HAPMAP CEU panel as tagging SNPs for the region, also several candidate SNPs were added. Some were both candidate as HAPMAP tagging SNPs.
2. Success rate of the genotyping.
3. Several SNPs could not be measured, one SNP had a low success rate and two SNPs were in perfect LD (r^2>0.9) with another SNP in these individuals and thus not included in the final analysis.
4. The P value resulting from a test for Hardy-Weinberg disequilibrium, significant threshold is P<0.002 because of multiple testing.

Table S11. The genotyping results for the INSIGF LD blocks

SNP	Source[1]	Success rate[2]	included?[3]	MAF(obs.)	MAF CEU		HW Pval[4]	associations (Pubmed [uid]: type)
rs11042594	tagging	98.3	no, covered by rs680 (r^2=0.90)	0.305	0.341	G:A	0.046	-
rs10840356	tagging	0	below <95%	-	-	-	-	-
rs4341514	tagging	100	out of HW P<0.002	0.471	0.442	T:C	3.14E-21	-
rs7873	tagging	100	YES	0.079	0.102	A:G	0.92	-
rs3802971	tagging	100	YES	0.092	0.099	C:T	0.69	-
rs680	candidate	100	YES	0.321	0.33 CEU 1000genomes	G:A	0.076	11448941: BMI adult men, 17289909: muscle functioning, 19434426: birth length, 10573016: body weight in men
rs3213223	candidate	100	YES	0.238	0.199	C:T	1.0	-
rs3213221	both	100	YES	0.412	0.434	C:G	0.11	17289909 :loss of strength following excercise, 17339271:association with IGF2 DMR methylation
rs3213216	tagging	99.2	no variance	0	0.345	G:G	1.0	-
rs3741212	tagging		no design poss.	-	-	-	-	-
rs11603378	tagging	0	below <95%	-	-	-	-	-
rs1003483	both	100	YES	0.424	0.46	T:G	0.0399	19390492: no association CTCF6 and H19DMR methylation, marginal association with paternal haplotype and SGA and placental growth, 17339271: IGF2 DMR methylation
rs1003484	candidate	100	covered by rs2239681 (r^2=1.0)	0.3	CEU 0.25 1000genomes	G:A	0.0035	17339271:methylation IGF2DMR
rs2239681	tagging	100	YES	0.3	0.27	G:A	0.0035	-
rs3741211	both	100	YES	0.374	0.389	A:G	0.0063	19546867: association IGF1BP1 levels, 21078522: endometrial cancer risk, 11448941: adult BMI, 17488802: adult height; 19390492: no association with CTCF6 and H19DMR methylation, marginal association with paternal haplotype transmission and SGA and placental growth

Table S11. (Continued A) The genotyping results for the INSIGF LD blocks

SNP	Source[1]	Success rate[2]	included?[3]	MAF(obs.)	MAF CEU		HW Pval[4]	associations (Pubmed [uid]: type)
rs3741209	candidate	100	covered by rs3741211 (r^2=1.0)	0.379	0.375	G:C	0.0043	18955703: abolishes CpG site in IGF2 DMR
rs3741206	tagging	no design poss.	-	-	-	-	-	
rs4320932	tagging	100	out of HW P<0.002	0.238	0.204	T:C	9.00E-04	-
rs10840442	tagging	no design poss.	-	-	-	-	-	
rs7924316	both	100	YES	0.438	0.465	T:G	0.32	17289909: strength loss following excercise
rs10840447	tagging	100	YES	0.392	0.376	C:T	0.017	-
rs3842756	tagging	100	YES	0.292	0.243	G:A	0.53	12610512: prostate cancer risk
rs689	candidate	100	YES	0.367	0.242	A:T	0.85	19434426: postnatal growth, 16608900: BMI in children, 17667841: paternal transmission associates with newborn IGF2 levels, 17700581: association with SGA risk, 15047631: head circumference at birth, newborn IGF2 levels, 10573016: body weight in men, 11101842: T2D, 11528401: paternal transmission with child BMI and insulin secretion, 9590300: birth size
rs3842738	candidate	100	no variance	0	0.0 CEU 1000genome	C:C	1	17667841: paternal haplotype transmission associates with newborn IGF2 levels, 17700581: paternal haplotype transmission associates with SGA risk

Table S12. Famine Associations corrected for genetic variation

Locus	Exp. –Unexp. (%)[2]		P
INSIGF	*-1.2*		*0.027*
IGF2 DMR0	*-1.9*		*6.8x10^{-6}*
IGF2 DMR1	*0.3*		*0.028*
IGF2 DMR2			
IGF2 DMR2 S.L.		0.4	0.78
IGF2 DMR2 CTCF		No	SNPs
H19 DMR	*No*		*SNPs*

Table S13. SNP associations with and without famine exposure correction

Association between	with famine exposure		without famine exposure	
***DMR* – SNP**	**beta**	**P**	**beta**	**P**
IGF2 DMR0-rs2239681	-1.3	1.1x10^{-3}	-1.4	9.9x10^{-4}
INSIGF-rs3842756	-2.0	8.2x10^{-6}	-2.1	1.4x10^{-5}
INSIGF-rs689	-2.3	7.4x10^{-8}	-2.4	4.0x10^{-8}

Supplement II

Table S1. Population and sequencing characteristics

Variable	Quantity
Individuals sequenced	48
Same-sex sibling controls	24
Age (SD)	58.3y (2.1)
Percentage of males	50%
Number of pre-war born sibling	12
Male pre-war born siblings	6
Median quality score reads (SD)	35.3 (2.0)
High quality reads million (SD)	25.6 (7.3)
Reads mapped uniquely (SD)	74.1%(10.7)
Bisulfite conversion (SD)	98.9%(0.7)

Table S2. Data filtering steps

Filtering steps	Total CpGs	CpGs matching
Total unique CpGs	3.174.757	
Random chromosome		3.195
Median Coverage <=5		1.296.450
Median Coverage >200		2.935
Median methylation = 0%		1.400.875
Median methylation = 100%		252.439
Total included unique CpGs*	1.206.149	

*Considerable numbers of CpG dinucleotides match multiple filtering criteria, resulting in a final number of included CpG dinucleotides higher than the subtraction of the 'CpGs matching' column form the total unique CpGs.

Figure S1. Histograms of the median coverage and success rate per CpG dinucleotide
Histogram of the median coverage (e.g. sequencing depth) over the 48 individuals of the CpG dinucleotides included in the analyses (N=1.206.149).
Histogram of the success rate for each CpG CpG dinucleotides included in the analyses for the 48 individuals.

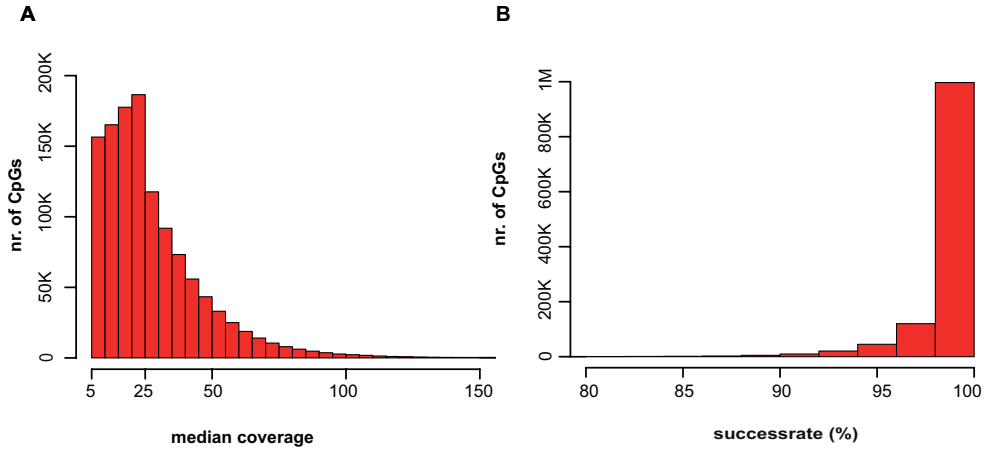


Figure S2. Density plot of the average methylation of the CpG dinucleotides

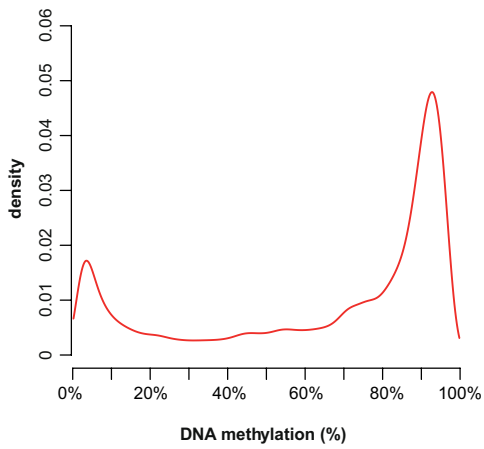
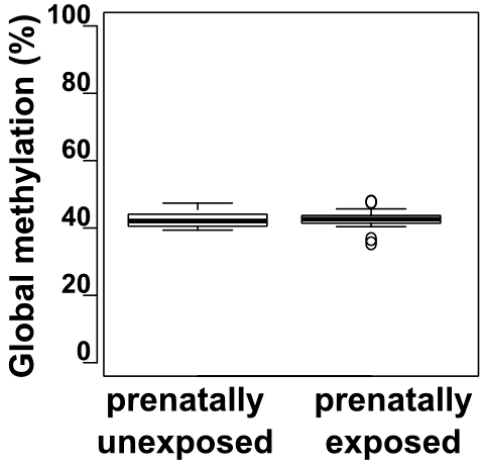


Figure S3. Global methylation



Boxplot depicting the global methylation levels of the prenatally exposed and unexposed siblings.

Table S3. Epityper associations with prenatal famine

Annotation		RRBS (N=48)				Epityper (N=48)	
Feature type[1]	Nearest Gene	Within pair diff. (%)	P[2]	P_{FDR}	correlation[3]	Within pair diff. (%)	P[4]
1	*DHRS4L2*	1.8	$3.0x10^{-9}$	$2.5x10^{-4}$	0.27	0.4	0.71
2	*EHD1*	-5.2	$5.7x10^{-9}$	$2.5x10^{-4}$	0.50	-4.0	$2.2x10^{-4}$
2	*DAPK2*	4.5	$1.1x10^{-8}$	$2.6x10^{-4}$	0.57	1.9	$6.4x10^{-3}$
2 & 3	*LOC554202*	6.5	$1.7x10^{-8}$	$2.6x10^{-4}$	0.52	3.5	$3.2x10^{-3}$
2	*LSM14B*	3.5	$1.7x10^{-8}$	$2.6x10^{-4}$	0.17	1.1	0.24
2	*ASS1*	-4.9	$4.8x10^{-8}$	$6.2x10^{-4}$	0.22	-0.5	0.42
2	*SMAD7*	4.2	$1.0x10^{-7}$	$1.1x10^{-3}$	0.78	4.7	$3.0x10^{-4}$
2 & 3	*CDH23*	4	$1.3x10^{-7}$	$1.1x10^{-3}$	0.73	3.9	$8.1x10^{-5}$
2	*MIR4315-1*	8.9	$2.1x10^{-7}$	$1.7x10^{-3}$	0.47	2.0	0.077
2	*ZIC1*	1.4	$3.2x10^{-7}$	$2.1x10^{-3}$	0.49	0.6	0.011
2	*INSR*	8.1	$3.9x10^{-6}$	0.01	0.72	3.9	0.018
2	*HOXD3*	3.2	$4.3x10^{-6}$	0.01	0.26	1.2	0.066
2	*RPTOR*	1.7	$9.1x10^{-6}$	0.02	0.63	8.6	$2.4x10^{-4}$
2 & 4	*RFTN1*	-2.3	$3.2x10^{-5}$	0.03	0.71	-1.9	$2.4x10^{-3}$
2	*STX1A*	3.7	$3.2x10^{-5}$	0.03	-0.17	1.1	0.17
2	*CPT1A*	4.5	$4.0x10^{-5}$	0.03	0.70	4.0	0.015
2	*SCARB1*	-10.5	$5.3x10^{-5}$	0.04	0.55	-4.9	$1.7x10^{-4}$
2	*KLF13*	-7.9	$6.1x10^{-5}$	0.04	0.79	-5.7	$7.9x10^{-4}$
2	*KLF6*	-6.2	$7.9x10^{-5}$	0.046	0.52	-2.6	$2.6x10^{-4}$

1 Type of genomic feature, 1 = non-CGI 'bonafide' promoter, 2 = Open chromatin, 3= enhancer, 4 = exon.

2 Two-sided P value resulting from a generalized linear mixed model where the analysis was weighted for sequencing depth.

3 The Pearson correlation between the average methylation of the RRBS region and the average of the CpG dinucleotides measured in the smaller region measured by Epityper.

4 The P value coming from a linear mixed model.

Table S4. Validation of the within pair differences in all 60 sibships with Epityper.

CDH23[1]	Meth. Exp(%)	SD(%)	Meth. Unexp(%)	SD(%)	Success rate (%)[2]	Diff.[3]	P[4]
CpG_1	24.8	5.6	22.4	6.1	100	2.3	0.0079
CpG_2	22.6	6.2	20.5	6.1	100	2.1	0.019
CpG_3	19.8	5.1	17.5	5.2	100	2.2	0.0048
CpG_4	22.5	6.1	20.1	6.3	100	2.3	0.0078
SMAD7							
CpG_1	23.7	6.9	20.6	7.1	95	3.0	0.0052
CpG_2	22.6	6.4	20.3	5.9	96.7	2.3	0.014
CpG_3	18.9	7.4	15.6	7.3	96.7	3.1	0.0077
CpG_4	14	5.8	10.6	5.9	94.2	3.3	0.0034
CpG_5.6	20.7	5.7	18.3	5.9	96.7	2.4	0.013
CpG_7	23	7.1	20.5	7.8	91.7	2.6	0.046
INSR							
CpG_2	33.5	5.6	30.6	5.8	95.8	2.9	0.0031
CpG_3	40	7.2	38	6	86.7	1.7	0.13
CpG_5	43.4	7.3	41.7	6.5	91.7	1.7	0.15
KLF13							
CpG_2	75.8	9.5	79.4	11.3	77.5	-3.7	0.07
CpG_4	65.4	7.8	68.4	8.6	99.2	-3.0	0.019
CpG_5	67.2	7.1	70.2	8.5	100	-2.9	0.016
CpG_6	64.2	7	67.4	9	100	-3.2	0.015
CpG_7	58.2	6.7	61.1	8.2	98.3	-2.8	0.020
CpG_9	62.3	7	65.5	8.5	98.3	-3.1	0.013
RFTN1							
CpG_1	89.6	3	90.3	3.1	100	-0.7	0.13
CpG_2	85	3.6	85.6	3.5	100	-0.7	0.19
CpG_3	81.5	3.7	82.8	3.5	100	-1.2	0.046
CpG_4	90.5	4.7	91.6	3.3	86.7	-0.9	0.23
CpG_5	82.3	2.8	83.2	2.7	100	-0.9	0.054
CpG_6.7	92.9	2.8	93.5	2.6	100	-0.6	0.21
CpG_8.9	84.1	3.8	85.2	5.1	100	-0.9	0.21
CpG_10	81.6	4.8	82.8	4.9	100	-1.2	0.12
CpG_12	81.8	4	83	4.2	100	-1.2	0.07
CPT1A							
CpG_2.3	41.3	10.9	39.1	11.2	99.2	2.4	0.09
CpG_5.6	58.1	8.9	56.3	8.9	99.2	1.9	0.11
CpG_8.9	76.5	3.8	75.4	4	99.2	1.1	0.05
CpG_10	49.1	8.8	46.9	8.7	99.2	2.4	0.032
CpG_12	34	8	31.7	8.8	99.2	2.4	0.037

1 The locus and individual CpG sites measured with Epityper after data filtering. The CpG dinucleotides are measured from the forward primer onward.

2 The success rate of the measurement in the 120 individuals

3 The average within pair differences in the 60 sib ships

4 The two-sided P-value resulting from a linear mixed model

Table S5. Epityper primers

NR[1]	Locus		Sequence
0	HUGO	Strand	FORWARD[3] (5'-3')
	coordinates(hg18)	T (°C)[2]	REVERSE[4] (5'-3')
1	DHRS4L2	-	GAGGATAGGGGTATTGGAGGTAAAG
	chr14:23,527,972-23,528,213	53	AAACCCAAACTTACTAATCTAATCCATA
2	EDH1	+	TTTGTTGTGAGGGAAATATAGTGATTG
	chr11:64,389,159-64,389,510	48	CCCTACCTTAATAAATACCAAAACCTAAA
3	DAPK2	-	TGATGATTTAATTTTGTGGGTTTGTGT
	chr15:62,062,839-62,063,043	53	AAATCCTAAAAACCCCACTCACAACT
4	LOC554202	+	AATTATTGGAGTGTAAAATTTTTTT
	chr9:21,595,548-21,595,759	48	CTATTTCCTAATAACCCATATTTAC
5	LSM14B	+	TTGTTTAGGAGGGTTTATTTTATGGTT
	chr20:60,141,366-60,141,715	53	ATAACAAACACTAACTCCCAAACTTCTAAC
6	ASS1	-	TGTTTTAGGGTGGGTATAGTTTAGGT
	chr9:132,344,966-132,345,523	46	ACCAAACCTCCTTAAAACTCTTCATA
7	SMAD7	+	TTGGGTTATATTTTATGTGTGGTGT
	chr18:44,677,194-44,677,679	53	CAACAACTAACTCTTTCCTACATCTAACT
8	CDH23	+	ATAGGGGAAGTTAGGTTTGGTAGAT
	chr10:73,227,653-73,227,914	53	ACTAAATAACCCTAATAAAACCCTC
9	miR4315-1	+	TTTTTTTTGTTTTTGATAGGGTTATG
	chr17:55,579,661-55,579,969	53	CCCAATATTCTAAATTCAAATCTTTACTCT
10	HIF1AN	-	AAAAGTGTTGATAGGGTTAGGAGAG
	chr10:102,319,419-102,319,893	Not working	TTTTATATATAACTTAATATAACAACATCA
11	ZIC1	+	TTTGGGTTTTTTGTTTTTAAGAGGT
	chr3:148,612,363-148,612,675	53	ACTTCCACCTAACTCCTAATTTCTAATTTT
C1	INSR	-	TTTTTAGGAGGTTTTTAGAGTTTTTAGATT
	chr19:7,110,140-7,110,418	44	CTAACCTCAAAATAATCCACCCCAC
C2	KLF13	-	AGGTAGGTATTTGTATAGAGGGGTTTA
	chr15:29,425,223-29,425,563	53	AAACTAACCACACCAAAACTTAATATACTT
C3	STX1A	+	GGTGAGGGGTTATAGATTAGGAGGT
	chr7:72,759,326-72,759,710	53	AAACAAACTAACCAAACAAACAAAACT
C4	RPTOR	-	GTTGGATGAGTAGGTTTTGGATGG
	chr17:76,479,050-76,479,293	46	CAATTCATAAAACAAAAAAAATTTAAAATA
C5	CPT1A	-	TTTAGGATATGGGTAAGTTTTGTTTTATAT
	chr11:68,286,598-68,286,810	48	AAATAATAACCTCCAAAAACCTTTTAAAAA
C6	RFTN1	+	TATGTATTTTTAAGGGGTTGTTTTT
	chr3:16,394,247-16,394,578	48	TAATATTATACCTCAATACCATTCCTCTAT
C7	HOXD3	+	TTTGGTGGTTTAATTTTGGTTAATT
	chr2:176,735,594-176,735,816	48	ATAAAAACATCCCCTCAAAAAAAA
C8	KLF6	-	AATAGTTTGAATTTAGATGTTAGTAG
	chr10:3,813,737-3,814,216	46	CCAAAACTAATACAATACAATAAC
C9	SCARB1	+	GGTGGTTAGGGTTAGTAAGAGAAGTA
	chr12:123,789,477-123,789,580	53	CCTATAACTCAAACTTCAAAAAAAAC

1 Primer pair number corresponding to the lowest p-value in RRBS (nr1-11; no reliable PCR was possible for nr10, chr10:102319110-102321355 [*HIF1AN*]) , several regions were chosen (C1-C9). Sequence of the forward PCR primer: for epiTYPER a tag with the following sequence is added 5': 5'-AGGAAGAGAG-sequence.

2 The annealing temperature in the PCR program: 15 min at 95°c, 15 minutes at 95°C, 4 rounds of 20 seconds at 95°C, 30 seconds at 65°C, 1 minute at 72°C; followed by 40 rounds, 20 seconds at 95°C, 30 seconds at ***Ann.T*** and 1 minute at 72°C; ending with 3 minute s at 72°C. The sequence of the reverse primer, for epiTYPER a tag with the following sequence is added 5': 5'-CAGTAATACGACTCACTATAGGGAGAAGGCT-sequence

Table S6. Number of CpG sites measured, and overlap between RRBS and Epityper measurement

Nearest Gene	location RRBS[1]	Location Epityper[2]	Nr CpGs RRBS	Nr CpGs Epityper	Nr CpGs overlapping
DHRS4L2	chr14:23,526,866-23,528,866	chr14:23,527,972-23,528,213	5	8	5
EHD1	chr11:64,374,355-64,390,875	chr11:64,389,159-64,389,510	26	9	8
DAPK2	chr15:62,060,557-62,063,275	chr15:62,062,839-62,063,043	7	12	2
LOC554202	chr9:21,594,650-21,595,650	chr9:21,595,548-21,595,759	3	3	2
LSM14B	chr20:60,141,215-60,146,975	chr20:60,141,366-60,141,715	7	6	3
ASS1	chr9:132,344,794-132,346,579	chr9:132,344,966-132,345,523	12	14	3
SMAD7	chr18:44,676,775-44,678,655	chr18:44,677,194-44,677,679	7	7	4
CDH23	chr10:73,227,550-73,228,550	chr10:73,227,653-73,227,914	3	4	3
miR4315	chr17:55,579,535-55,580,790	chr17:55,579,661-55,579,969	3	6	3
ZIC1	chr3:148,611,075-148,612,495	chr3:148,612,363-148,612,675	21	14	5
INSR	chr19:7,110,011-7,111,334	chr19:7,110,140-7,110,418	2	3	2
KLF13	chr15:29,423,875-29,427,520	chr15:29,425,223-29,425,563	8	6	6
STX1A	chr7:72,758,075-72,760,255	chr7:72,759,326-72,759,710	7	8	4
RPTOR	chr17:76,471,363-76,483,344	chr17:76,479,050-76,479,293	45	6	3
CPT1A	chr11:68,285,186-68,289,024	chr11:68,286,598-68,286,810	15	8	7
RFTN	chr3:16,394,228-16,394,613	chr3:16,394,247-16,394,578	10	11	5
HOXD3	chr2:176,734,540-176,735,745	chr2:176,735,594-176,735,816	7	6	2
KLF6	chr10:3,810,815-3,816,315	chr10:3,813,737-3,814,216	20	18	10
SCARB1	chr12:123,788,495-123,792,067	chr12:123,789,477-123,789,580	6	6	4

1 Genomic location of the genomic feature

2 Genomic location of the Epityper PCR amplicon

Table S7. Neutrophil variation and DNA methylation at the P-DMRs

P-DMR	Beta[1] (%methylation/ %neutrophils)	P[2]	SD change required to explain famine association[3]
SMAD7	-0.19	0.17	-5.1
CDH23	-0.35	$3.1x10^{-3}$	-1.9
INSR	0.02	0.91	31.4
CPT1A	-0.51	0.11	-1.2
KLF13	0.33	0.08	-2.8
RFTN1	0.00	0.99	∞

1 The effect size of the association of the percentage of neutrophils in blood with methylation in 44 unrelated individuals from the control population in the Leiden Longevity Study.

2 Two-sided p-value for the association between DNA methylation and the percentage of neutrophils in blood.

3 The size of the change in neutrophil percentage in blood, expressed in standard deviations (SD), required to explain in full the association between DNA methylation and prenatal famine exposure (3.3% change in neutrophils is 1 SD change).

4 Only CDH23 is affected by blood cell heterogeneity, but the change in blood cell composition to explain the observed famine association is so large (~2SD) that this is a highly unlikely explanation.