Environmental Health Perspectives doi:10.1289/ehp.1206068

Supplemental Material

Genetic and Non-genetic Predictors of LINE-1 Methylation in Leukocyte DNA

Salman M. Tajuddin[1], André F. S. Amaral[1], Agustín F. Fernández[2], Sandra Rodríguez-Rodero[2], Ramón María Rodríguez[2], Lee E. Moore[3], Adonina Tardón[4], Alfredo Carrato[5,6], Montserrat García-Closas[7], Debra T. Silverman[3], Brian P. Jackson[8], Reina García-Closas[9], Ashley L. Cook[1], Kenneth P. Cantor[10], Stephen Chanock[3], Manolis Kogevinas[11], Nathaniel Rothman[3], Francisco X. Real[12,13], Mario F. Fraga[2,14*], Núria Malats[1*] for the Spanish Bladder Cancer (SBC)/EPICURO Study investigators[15]

[1]Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

[2]Cancer Epigenetics Laboratory, Instituto Universitario de Oncología del Principado de Asturias (IUOPA), HUCA, Universidad de Oviedo, Oviedo, Spain

[3]National Cancer Institute, Bethesda, Maryland, USA

[4]Universidad de Oviedo, Oviedo, Spain

[5]Hospital General Universitario de Elche, Elche, Spain

[6]Hospital Ramon y Cajal, Madrid, Spain

[7]Division of Genetics and Epidemiology, Institute of Cancer Research, Sutton, United Kingdom

[8]Trace Element Analysis Core, Department of Earth Sciences, Dartmouth College, Hanover, New Hampshire, USA

[9]Unidad de Investigación, Hospital Universitario de Canarias, La Laguna, Spain

[10]KP Cantor Environmental LLC, Silver Spring, Maryland, USA

[11]Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

[12]Epithelial Carcinogenesis Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

[13]Departament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra, Barcelona, Spain

[14]Department of Immunology and Oncology, Centro Nacional de Biotecnología/CNB-CSIC, Cantoblanco, Madrid, Spain

[15]Spanish Bladder Cancer (SBC)/EPICURO Study investigators are listed in Appendix 1

* Co-last authors contributed equally to this work.

Address Correspondence to:

Núria Malats, M.D., Ph.D.
Genetic and Molecular Epidemiology Group
Spanish National Cancer Research Centre (CNIO)
C/ Melchor Fernández Almagro, 3
28029 Madrid, Spain
Phone: +34-912-246-900 (ext. 3330)
Fax: +34-912-246-911
E-mail: nmalats@cnio.es

Table of Contents Page

Supplemental Material, Table S1. List of genes involved in the one-carbon metabolism pathway selected for the present study

Chromosome location	**Gene symbol [ID]^a**	**Gene name**	**Gene function**
1p31.1	*CTH*	Cystathionase	Converts cystathione derived from methionine into cysteine.
1p36.3	*MTHFR*	Methylenetetrahydrofolate reductase (NAD(P)H)	Catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.
1q43	*MTR*	5-methyltetrahydrofolate-homocysteine methyltransferase	Catalyzes the final step in methionine biosynthesis.
2p23	*DNMT3A*	DNA (cytosine-5-)-methyltransferase 3 alpha	Functions in de novo methylation of cytosine residues.
2q35	*ATIC*	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP(inosine monophosphate) cyclohydrolase	Catalyzes the last two steps of the de novo purine biosynthetic pathway. The N-terminal domain has phosphoribosylaminoimidazolecarboxamide formyltransferase activity, and the C-terminal domain has IMP cyclohydrolase activity.
3p21.1	*CHDH*	Choline dehydrogenase	Encodes a protein that localizes to the mitochondrion. Variations in this gene can affect susceptibility to choline deficiency.
3q21.3	*ALDH1L1*	Aldehyde dehydrogenase 1 family, member L1	Catalyzes the conversion of 10-formyltetrahydrofolate, NADP, and water to tetrahydrofolate, NADPH, and carbon dioxide.
5p15.31	*MTRR*	5-methyltetrahydrofolate-homocysteine methyltransferase reductase	Regenerates a functional methionine synthase via reductive methylation
5q11.2-q13.2	*DHFR*	Dihydrofolate reductase	Converts dihydrofolate into tetrahydrofolate, a methyl group shuttle required for the de novo synthesis of purines, thymidylic acid, and certain amino acids.
5q13.1-q15	*BHMT*	Betaine-homocysteine S-methyltransferase	Catalyzes the conversion of betaine and homocysteine to dimethylglycine and methionine, respectively.
6p12	*GNMT*	Glycine N-methyltransferase	Catalyzes the conversion of S-adenosyl-L-methionine (along with glycine) to S-adenosyl-L-homocysteine and sarcosine.

Chromosome location	**Gene symbol [ID][a]**	**Gene name**	**Gene function**
10q24.32	*AS3MT*	Arsenic (+3 oxidation state) methyltransferase	Catalyzes the transfer of a methyl group from S-adenosyl-L-methionine to trivalent arsenical and play a role in arsenic metabolism.
11p11.2	*FOLH1*	Folate hydrolase (prostate-specific membrane antigen)1/glutamate carboxypeptidase II/	Acts as a glutamate carboxypeptidase on different alternative substrates, including the nutrient folate and the neuropeptide N-acetyl-l-aspartyl-l-glutamate.
14q24	*MTHFD*	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1	Catalyzes one of three sequential reactions in the interconversion of 1-carbon derivatives of tetrahydrofolate.
15q25.1	*MTHFS*	5,10-methenyltetrahydrofolate synthetase	Catalyzes the conversion of 5-formyltetrahydrofolate to 5,10-methenyltetrahydrofolate, a precursor of reduced folates involved in 1-carbon metabolism.
17p11.2	*PEMT*	Phosphatidylethanolamine N-methyltransferase	Converts phosphatidylethanolamine to phosphatidylcholine by sequential methylation in the liver.
17p11.2	*SHMT1*	Serine hydroxymethyltransferase 1	Catalyzes the reversible conversion of serine and tetrahydrofolate to glycine and 5,10-methylene tetrahydrofolate. This reaction provides one carbon units for synthesis of methionine, thymidylate, and purines in the cytoplasm.
18p11.32	*TYMS*	Thymidylate synthetase	Catalyzes the methylation of deoxyuridylate to deoxythymidylate using 5,10-methylenetetrahydrofolate as a cofactor.
19p13.2	*DNMT1*	DNA (cytosine-5-)-methyltransferase 1	Establishes and regulates tissue-specific patterns of methylated cytosine residues.
20q11.2	*DNMT3B*	DNA (cytosine-5-)-methyltransferase 3 beta	Functions in de novo methylation of cytosine residues.
21q22.1; 21q22.11	*GART*	Glycinamide ribonucleotide transformylase	Encodes a protein that has phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase activity which is required for de novo purine biosynthesis.
21q22.3	*CBS*	Cystathionine-beta-synthase	Acts as a homotetramer to catalyze the conversion of homocysteine to cystathionine, the first step in the

Chromosome location	**Gene symbol [ID][a]**	**Gene name**	**Gene function**
			transsulfuration pathway.
21q22.3	*SLC19A1*	Solute carrier family 19 (folate transporter), member 1	Transports folate and is involved in the regulation of intracellular concentrations of folate.
22q12.2	*TCN2*	Transcobalamin II	Binds and mediates the transport of vitamin B12 into cells.

[a] Maglott D, Ostell J, Pruitt KD, Tatusova T. 2005. Entrez Gene: gene-centered information at NCBI. Nucleic Acids Res 33:D54-D58.

Supplemental Material, Table S2. Distribution of SNPs studied in the present study by genotyping platform.

This table is provided as a separate Excel file.

Supplemental Material, Table S3. List of single nucleotide polymorphisms with significant Fisher's exact test selected for further analysis (p-value ≤ 0.05)

dbSNP Identifier	N	MAF	Chromosome	Location[a]	Gene	Region in the gene	P-HWE	Fisher's exact test p-value[b]
rs11683424	875	0.12	2	25342636	*DNMT3A*	Intron	0.20	0.006
rs7581217	875	0.39	2	25378448	*DNMT3A*	Intron	0.62	0.002
rs1550117	875	0.08	2	25419411	*DNMT3A*	Flanking 5'UTR	0.81	0.009
rs4369857	875	0.04	2	215841917	*ATIC*	Flanking 5'UTR	1.00	0.02
rs7563206	874	0.47	2	215898899	*ATIC*	Intron	0.84	0.04
rs1880586	875	0.47	2	215903416	*ATIC*	Intron	0.89	0.04
rs4673991	875	0.32	2	215920334	*ATIC*	Intron	0.31	0.004
rs4673993	875	0.32	2	215920584	*ATIC*	Intron	0.31	0.004
rs4672768	873	0.32	2	215922369	*ATIC*	Intron	0.31	0.005
rs10498036	875	0.40	2	215922737	*ATIC*	Flanking 3'UTR	0.57	0.004
rs7604984	875	0.40	2	215925884	*ATIC*	Flanking 3'UTR	0.62	0.003
rs7085104	875	0.38	10	104618863	*AS3MT*	Flanking 5'UTR	1.00	0.02
rs1077965	875	0.41	15	77852392	*MTHFS*	Flanking 3'UTR	0.58	0.007
rs11855092	875	0.24	15	77877293	*MTHFS*	Flanking 3'UTR	0.31	0.03
rs1380642	875	0.18	15	77883926	*MTHFS*	Flanking 3'UTR	0.57	0.01
rs4646340	875	0.37	17	17434740	*PEMT*	Intron	0.51	0.04
rs7215833	875	0.36	17	17448033	*PEMT*	Flanking 5'UTR	0.51	0.02
rs914238	875	0.49	21	45840089	*SLC19A1*	Flanking 5'UTR	0.89	0.002
rs2838965	873	0.42	21	45846212	*SLC19A1*	Flanking 5'UTR	0.33	0.02
rs9606756	875	0.12	22	29336860	*TCN2*	Exon	0.87	0.005
rs9621049	875	0.11	22	29343419	*TCN2*	Exon	0.86	0.02
rs4820887	875	0.10	22	29346914	*TCN2*	Intron	0.85	0.01

MAF, minor allele frequency. P-HWE, Chi-square test p-value for Hardy-Weinberg equilibrium.

[a] Human Genome Build 36.3 location.

[b] Fisher's exact test p-value from comparison of categorical variables LINE-1 methylation in tertiles (<56.7%, 56.7–58.6%, and >58.6%) and SNPs modeled according to codominant mode of in heritance coded as "0" for wild type, "1" heterozygous variant, "2" for homozygous variant.

Supplemental Material, Table S4. Distributional characteristics of study subjects and LINE-1 methylation in the SBC/EPICURO Study

Variables	N	Percent	LINE-1 methylation (%) Median (IQR)	P-value[a]
Age (years)				
<60	253	28.4	57.4 (3.7)	0.9
60-69	342	38.3	57.4 (3.2)	
70+	297	33.3	57.5 (3.2)	
Gender				
Male	792	88.8	57.5 (3.3)	0.04
Female	100	11.2	57.1 (3.2)	
Region				
Barcelona	168	18.8	57.5 (3.0)	0.1
Vallès	135	15.1	57.1 (2.6)	
Elche	73	8.2	57.1 (2.5)	
Tenerife	145	16.3	57.3 (3.2)	
Asturias	371	41.6	57.7 (3.9)	
Body mass index (kg/m^2)				
<25.0	372	53.4	57.4 (3.3)	0.9
25.0-26.99	148	21.2	57.4 (3.7)	
27.0-29.99	120	17.2	57.5 (3.2)	
≥30.0	57	8.2	57.6 (3.5)	
Missing data	195			
Smoking status				
Non-smoker	255	28.7	57.4 (3.2)	0.2
Occasional smoker	66	7.4	58.0 (3.3)	
Former smoker	329	37.0	57.4 (3.3)	
Current smoker	239	26.9	57.4 (3.7)	
Missing data	3			
Tobacco type				
Non-smoker	255	31.0	57.4 (3.2)	0.2
Blond only	99	12.0	57.0 (3.2)	
Black only	219	26.5	57.7 (3.6)	
Blond and black	154	18.7	57.3 (3.6)	
Unknown	97	11.8	57.7 (3.0)	
Missing data	68			
Controls' diagnosis				
Hernia	332	37.2	57.4 (3.1)	0.8
Fracture & Trauma	263	29.5	57.5 (4.0)	
Hydrocele	122	13.7	57.6 (3.3)	
Other Abdominal Surgery	99	11.1	57.2 (2.9)	

Variables	N	Percent	LINE-1 methylation (%) Median (IQR)	P-value[a]
Other Diseases	76	8.5	57.6 (3.8)	
Vitamin B1 intake (µg/day/kcal)				
< 0.66	323	50.1	57.5 (3.8)	0.4
≥0.66	322	49.9	57.4 (3.3)	
Missing data	247			
Vitamin B2 intake (µg/day/kcal)				
< 0.91	323	50.1	57.4 (3.7)	0.9
≥0.91	322	49.9	57.5 (3.6)	
Missing Data	247			
Vitamin B3 intake (µg/day/kcal)				
<10.08	323	50.1	57.5 (3.9)	0.5
≥10.08	322	49.9	57.4 (3.3)	
Missing Data	247			
Vitamin B6 intake (µg/day/kcal)				
<1.00	323	50.1	57.4 (3.9)	0.5
≥1.00	322	49.9	57.4 (3.4)	
Missing Data	247			
Vitamin B12 intake (µg/day/kcal)				
<3.98	323	50.1	57.4 (3.7)	0.8
≥3.98	322	49.9	57.4 (3.6)	
Missing Data	247			
Folate intake (µg/day/kcal)				
<166.74	323	50.1	57.4 (3.9)	0.5
≥166.74	322	49.9	57.5 (3.3)	
Missing Data	247			
Protein intake (µg/day/kcal)				
<46.68	323	50.1	57.4 (3.7)	0.97
≥4.33	322	49.9	57.4 (3.6)	
Missing Data	247			
Alcohol intake (µg/day/kcal)				
<4.33	323	50.1	57.4 (3.6)	0.4
≥4.33	322	49.9	57.4 (3.8)	
Missing Data	247			
Fruit intake (g/day/kcal)				
<172.71	320	50.1	57.3 (3.2)	0.6
≥172.71	319	49.9	57.6 (4.2)	
Missing Data	253			
Vegetable intake (g/day/kcal)				
<107.12	320	50.0	57.3 (4.0)	0.3

Variables	N	Percent	LINE-1 methylation (%) Median (IQR)	P-value[a]
≥107.12	320	50.0	57.6 (3.3)	
Missing Data	252			
Fruit and vegetable intake (g/day/kcal)				
<295.61	320	50.1	57.4 (3.5)	0.9
≥295.61	319	49.9	57.4 (3.9)	
Missing Data	253			
Toenail aluminum (µg/g)				
< 10.51	329	50.0	57.5 (3.6)	0.5
≥ 10.51	329	50.0	57.4 (3.3)	
Missing Data	234			
Toenail arsenic (µg/g)				
<0.07	330	50.1	57.5 (3.8)	0.7
≥0.07	329	49.9	57.4 (3.3)	
Missing Data	233			
Toenail cadmium (µg/g)				
<0.01	330	50.1	57.5 (3.2)	0.4
≥0.01	329	49.9	57.4 (3.6)	
Missing Data	233			
Toenail chromium (µg/g)				
< 0.41	330	50.1	57.5 (3.8)	0.6
≥ 0.41	329	49.9	57.4 (3.2)	
Missing Data	233			
Toenail copper (µg/g)				
< 3.38	329	49.9	57.5 (3.3)	0.9
≥3.38	330	50.1	57.4 (3.5)	
Missing Data	233			
Toenail iron (µg/g)				
< 14.61	329	50.0	57.4 (3.1)	0.3
≥ 14.61	329	50.0	57.6 (3.7)	
Missing Data	234			
Toenail lead (µg/g)				
<0.40	329	50.1	57.5 (3.1)	0.7
≥0.40	330	49.9	57.4 (3.6)	
Missing Data	233			
Toenail manganese (µg/g)				
< 0.33	330	50.1	57.4 (3.3)	0.9
≥ 0.33	329	49.9	57.5 (3.6)	
Missing Data	233			
Toenail nickel (µg/g)				

Variables	**N**	**Percent**	**LINE-1 methylation (%) Median (IQR)**	**P-value[a]**
< 0.47	329	49.9	57.5 (3.0)	0.8
≥ 0.47	330	50.1	57.4 (3.9)	
Missing Data	233			
Toenail selenium (µg/g)				
<0.56	330	50.1	57.4 (3.4)	0.6
≥0.56	329	49.9	57.5 (3.5)	
Missing Data	233			
Toenail vanadium (µg/g)				
< 0.02	326	50.1	57.5 (3.7)	0.6
≥ 0.02	325	49.9	57.4 (3.3)	
Missing Data	241			
Toenail zinc (µg/g)				
< 103.20	329	49.9	57.5 (3.3)	0.8
≥103.20	330	50.1	57.4 (3.7)	
Missing data	233			
***NAT2* phenotype**				
Rapid/Intermediate acetylator	389	43.9	57.4 (3.5)	0.8
Slow acetylator	498	56.1	57.5 (3.2)	
Missing data	5			
***GSTM1* genotype**				
(+/+, +/-)	421	47.7	57.4 (3.5)	0.6
(-/-)	462	52.3	57.5 (3.1)	
Missing data	9			
***GSTT1* genotype**				
(+/+, +/-)	688	77.7	57.5 (3.3)	0.2
(-/-)	198	22.3	57.4 (3.3)	
Missing data	6			

IQR, interquartile range.

[a] P-value from the Kruskal-Wallis test.

Supplemental Material, Table S5. Association between LINE-1 methylation and individual characteristics of study subjects in the SBC/EPICURO Study

Variables	**N**	**β[a] (95% CI)**	**P-value**
Age (years)	892	-0.004 (-0.02, 0.01)	0.6
Gender			
Male	792	Ref	
Female	100	-0.5 (-1.0, 0.04)	0.07
Region			
Barcelona	168	Ref	
Vallès	135	-0.2 (-0.7, 0.4)	0.6
Elche	73	-0.5 (-1.1, 0.2)	0.2
Tenerife	145	-0.1 (-0.7, 0.4)	0.6
Asturias	371	0.2 (-0.3, 0.6)	0.5
Body mass index (kg/m²)			
<25.0	372	Ref	
25.0-26.99	148	-0.1 (-0.6, 0.3)	0.5
27.0-29.99	120	0.2 (-0.3, 0.7)	0.3
≥30.0	57	0.007 (-0.7, 0.7)	0.9
Missing data	195		
Controls' diagnosis			
Hernia	332	Ref	
Fracture & Trauma	263	-0.04 (-0.5, 0.4)	0.8
Hydrocele	122	0.2 (-0.4, 0.7)	0.5
Other Abdominal Surgery	99	0.1 (-0.7, 0.4)	0.6
Other Diseases	76	0.2 (-0.4, 0.8)	0.6
Dietary intake[b]			
Vitamin B1 (µg/day/kcal)	645	0.6 (-0.5, 1.8)	0.3
Vitamin B2 (µg/day/kcal)	645	0.2 (-0.5, 0.9)	0.6
Vitamin B3 (µg/day/kcal)	645	0.03 (-0.04, 0.1)	0.4
Vitamin B6 (µg/day/kcal)	645	0.8 (0.01, 1.7)	0.05
Vitamin B12 (µg/day/kcal)	645	-0.03 (-0.08, 0.02)	0.2
Folate (µg/day/kcal)	645	0.002 (-0.001, 0.01)	0.1
Protein (µg/day/kcal)	645	0.01 (-0.01, 0.03)	0.3
Alcohol (µg/day/kcal)	645	-0.01 (-0.03, 0.02)	0.5
Fruit (g/day/kcal)	639	0.0001 (-0.001, 0.002)	0.9
Vegetable (g/day/kcal)	640	0.002 (-0.0004, 0.004)	0.1
Fruit and vegetable (g/day/kcal)	639	0.001 (-0.001, 0.002)	0.4
Toenail trace elements[c]			
Aluminium (µg/g)	658	-0.003 (-0.01, 0.002)	0.2
Arsenic (µg/g)	659	-3.3 (-5.7, -1.0)	0.006
Cadmium (µg/g)	659	0.1 (-0.3, 0.6)	0.7

Variables	N	β[a] (95% CI)	P-value
Chromium (µg/g)	659	-0.01 (-0.05, 0.03)	0.7
Copper (µg/g)	659	-0.01 (-0.06, 0.05)	0.8
Iron (µg/g)	658	0.002 (0.001, 0.004)	0.008
Lead (µg/g)	659	-0.05 (-0.1, 0.03)	0.2
Manganese (µg/g)	659	-0.05 (-0.2, 0.06)	0.4
Nickel (µg/g)	659	0.02 (0.01, 0.03)	0.004
Selenium (µg/g)	659	0.4 (-0.6, 1.3)	0.4
Vanadium (µg/g)	651	-0.8 (-2.9, 1.3)	0.4
Zinc (µg/g)	659	-0.001 (-0.004, 0.001)	0.4
***NAT2* phenotype**			
Rapid/Intermediate	389	Ref	
Slow	498	0.2 (-0.1, 0.5)	0.2
Missing data	5		
***GSTM1* genotype**			
(+/+, +/-)	421	Ref	
(-/-)	462	0.02 (-0.3, 0.3)	0.9
Missing data	9		
***GSTT1* genotype**			
(+/+, +/-)	688	Ref	
(-/-)	198	-0.2 (-0.6, 0.2)	0.4
Missing data	6		

[a] Adjusted for age, gender, and region.

[b] Data available for those who completed food frequency questionnaire.

[c] Data available for those who provided toe nail for trace element assessment.

Note: the exposure contrast for trace elements is 1-µg/g and for dietary variables is 1-µg/day/kcal.

Supplemental Material, Table S6. Association between LINE-1 methylation and 15 single nucleotide polymorphisms in genes involved in the one-carbon metabolism pathway with nonsignificant results.

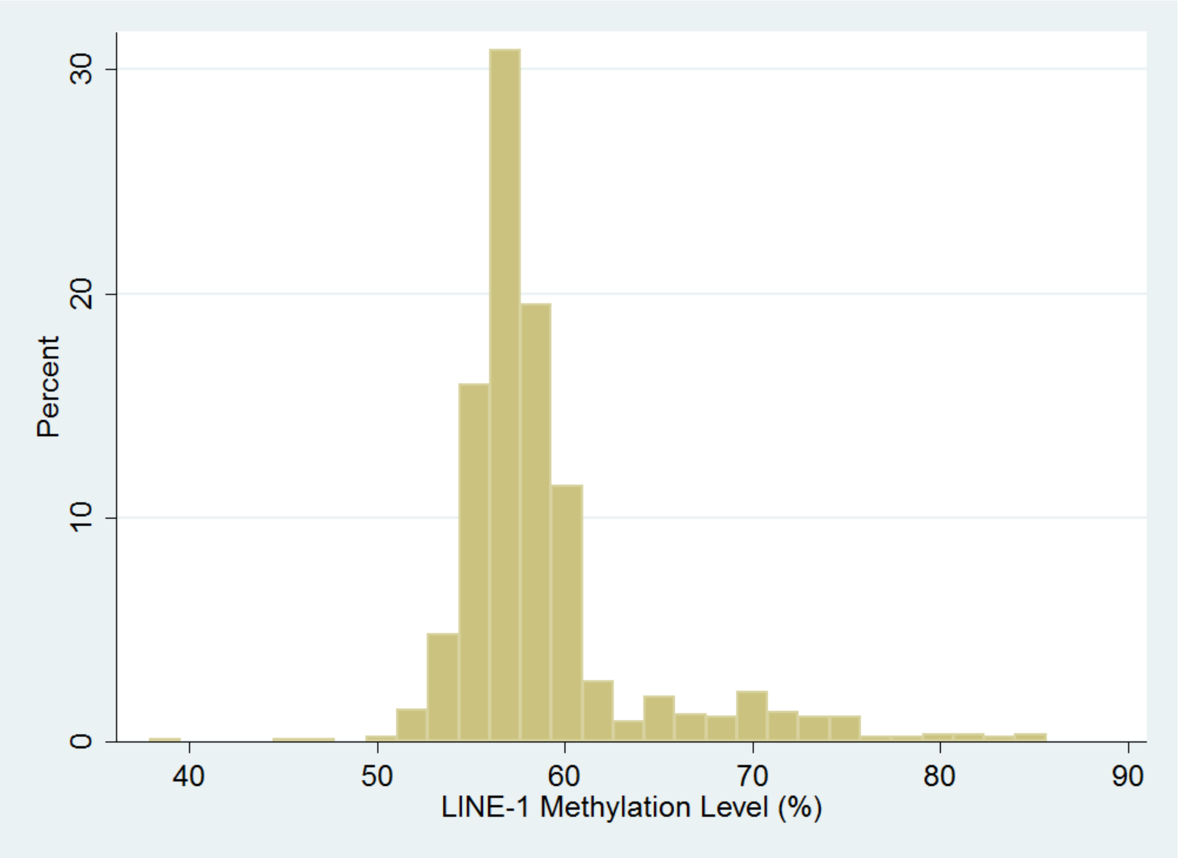
This table is provided as a separate Excel file.

Supplemental Material, Table S7. Multivariable model of association between LINE-1 methylation and individual characteristics, toenail trace elements and single nucleotide polymorphisms among study subjects in the SBC/EPICURO Study

Variable	**N**	**β[a] (95% CI)**	**P-value**	**Global p-value[b]**
Age (years)	601	-0.01 (-0.03, 0.01)	0.2	
Gender				
Male	534	Ref		
Female	67	-1.0 (-1.7, -0.3)	0.006	
Region				
Barcelona	131	Ref		
Valles	90	-0.05 (-0.7, 0.6)	0.9	
Elche	57	-0.4 (-1.2, 0.3)	0.3	
Tenerife	82	0.2 (-0.5, 0.9)	0.5	
Asturias	241	0.1 (-0.4, 0.7)	0.6	
Tobacco Type				
Non-smoker	187	Ref		
Blond only	76	-0.5 (-1.2, 0.2)	0.1	
Black only	156	0.09 (-0.5, 0.7)	0.7	
Blond and black	118	-0.6 (-1.2, 0.05)	0.07	
Unknown	64	-0.07 (-0.8, 0.7)	0.9	
Toenail Trace Element				
Arsenic (µg/g)	601	-4.8 (-7.8, -1.8)	0.002	
Iron (µg/g)	601	0.003 (0.001, 0.01)	0.0004	
Nickel (µg/g)	601	0.01 (0.004, 0.03)	0.005	
Gene, dbSNP identifier				
***DNMT3A*-rs7581217,** C>T	601	0.3 (0.003, 0.6)	0.048	
***AS3MT*-rs7085104**				
AA/AG	518	Ref		
GG	83	0.5 (-0.07, 1.1)	0.09	
***MTHFS*-rs1380642**				
CC	409	Ref		
CT	167	0.4 (-0.02, 0.9)	0.06	0.005
TT	25	-1.2 (-2.2, -0.2)	0.02	
***SLC19A1*-rs914238**				
TT	159	Ref		
TC	293	0.3 (-0.1, 0.8)	0.2	0.07
CC	149	-0.2 (-0.8, 0.3)	0.5	
***TCN2*-rs9621049**				
CC/CT	593	Ref		
TT	8	4.3 (0.9, 7.6)	0.01	
***TCN2*-rs9606756**				
AA/AG	594	Ref		
GG	7	-2.3 (-7.1, 2.5)	0.3	
***TCN2*-rs4820887**				
GG/GA	595	Ref		
AA	6	-0.6 (-6.7, 5.6)	0.9	

[a] Fully adjusted robust regression coefficient.

[b] Global p-value was estimated by using a two-degrees of freedom likelihood-ratio test.



Supplemental Material, Figure S1. Distribution of LINE-1 methylation among study subjects in the SBC/EPICURO study.