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References

1. Vaartjes I, Koopman C, van Dis I, Visseren FLJ, and Bots ML (2013) Hart- en vaatziekten in Nederland. In: Vaartjes I, Koopman C, van Dis I, Visseren FLJ, Bots ML, editors. Hart- en vaatziekten in Nederland, 2013, cijfers over leefstijl, risicofactoren, ziekte en sterfte. Den Haag: Hartstichting. pp. 7-26.
2. Dermitzakis ET and Clark AG (2009) Genetics. Life after GWA studies. *Science* 326: 239-240.
3. Mechanic LE, Chen HS, Amos CI, Chatterjee N, Cox NJ, Divi RL, et al. (2011) Next generation analytic tools for large scale genetic epidemiology studies of complex diseases. *Genet Epidemiol* .
4. Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, and de Faire U (2002) Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins. *J Intern Med* 252: 247-254.
5. Brunham LR and Hayden MR (2013) Hunting human disease genes: lessons from the past, challenges for the future. *Hum Genet* 132: 603-617.
6. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, and Kannel WB (1998) Prediction of coronary heart disease using risk factor categories. *Circulation* 97: 1837-1847.
7. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. (2007) European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). *Eur Heart J* 28: 2375-2414.

8. Barker DJ and Osmond C (1986) Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1: 1077-1081.
9. Leon DA, Lithell HO, Vagero D, Koupilova I, Mohsen R, Berglund L, Lithell UB, and McKeigue PM (1998) Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915-29. *BMJ* 317: 241-245.
10. Lumey LH, Stein AD, and Susser E (2011) Prenatal famine and adult health. *Annu Rev Public Health* 32: 237-262.
11. Lumey LH, Stein AD, Kahn HS, van der Pal-de Bruin KM, Blauw G, Zybert PA, and Susser ES (2007) Cohort Profile: the Dutch Hunger Winter Families Study. *Int J Epidemiol* 36: 1196-1204.
12. Weaver IC (2007) Epigenetic programming by maternal behavior and pharmacological intervention. Nature versus nurture: let's call the whole thing off. *Epigenetics* 2: 22-28.
13. Bogdarina I, Welham S, King PJ, Burns SP, and Clark AJ (2007) Epigenetic modification of the renin-angiotensin system in the fetal programming of hypertension. *Circ Res* 100: 520-526.
14. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, and Lumey LH (2008) Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A* 105: 17046-17049.
15. Feil R and Fraga MF (2011) Epigenetics and the environment: emerging patterns and implications. *Nat Rev Genet* 13: 97-109.
16. Winnefeld M and Lyko F (2012) The aging epigenome: DNA methylation from the cradle to the grave. *Genome Biol* 13: 165.

17. Feinberg AP (2008) Epigenetics at the epicenter of modern medicine. *JAMA* 299: 1345-1350.
18. Feinberg AP (2013) The epigenetic basis of common human disease. *Trans Am Clin Climatol Assoc* 124: 84-93.
19. Tremethick DJ (2007) Higher-order structures of chromatin: the elusive 30 nm fiber. *Cell* 128: 651-654.
20. Misteli T (2007) Beyond the sequence: cellular organization of genome function. *Cell* 128: 787-800.
21. Zhou VW, Goren A, and Bernstein BE (2011) Charting histone modifications and the functional organization of mammalian genomes. *Nat Rev Genet* 12: 7-18.
22. Kouzarides T (2007) Chromatin modifications and their function. *Cell* 128: 693-705.
23. Bernstein BE, Meissner A, and Lander ES (2007) The mammalian epigenome. *Cell* 128: 669-681.
24. Suzuki MM and Bird A (2008) DNA methylation landscapes: provocative insights from epigenomics. *Nat Rev Genet* 9: 465-476.
25. Cedar H and Bergman Y (2009) Linking DNA methylation and histone modification: patterns and paradigms. *Nat Rev Genet* 10: 295-304.
26. Li B, Carey M, and Workman JL (2007) The role of chromatin during transcription. *Cell* 128: 707-719.
27. Bestor TH (2003) Cytosine methylation mediates sexual conflict. *Trends Genet* 19: 185-190.
28. Jones PA (2012) Functions of DNA methylation: islands, start sites, gene bodies and beyond. *Nat Rev Genet* 13: 484-492.

29. Jaenisch R and Bird A (2003) Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet* 33 Suppl: 245-254.
30. Reik W (2007) Stability and flexibility of epigenetic gene regulation in mammalian development. *Nature* 447: 425-432.
31. Reik W and Walter J (2001) Genomic imprinting: parental influence on the genome. *Nat Rev Genet* 2: 21-32.
32. Ferguson-Smith AC (2011) Genomic imprinting: the emergence of an epigenetic paradigm. *Nat Rev Genet* 12: 565-575.
33. Plagge A and Kelsey G (2006) Imprinting the Gnas locus. *Cytogenet Genome Res* 113: 178-187.
34. Constancia M, Kelsey G, and Reik W (2004) Resourceful imprinting. *Nature* 432: 53-57.
35. Weaver JR, Susiarjo M, and Bartolomei MS (2009) Imprinting and epigenetic changes in the early embryo. *Mamm Genome* 20: 532-543.
36. Shemer R, Hershko AY, Perk J, Mostoslavsky R, Tsuberi B, Cedar H, Buiting K, and Razin A (2000) The imprinting box of the Prader-Willi/Angelman syndrome domain. *Nat Genet* 26: 440-443.
37. Smith AC, Choufani S, Ferreira JC, and Weksberg R (2007) Growth regulation, imprinted genes, and chromosome 11p15.5. *Pediatr Res* 61: 43R-47R.
38. Hashimoto H, Vertino PM, and Cheng X (2010) Molecular coupling of DNA methylation and histone methylation. *Epigenomics* 2: 657-669.
39. Miranda TB and Jones PA (2007) DNA methylation: the nuts and bolts of repression. *J Cell Physiol* 213: 384-390.

40. Ramsahoye BH, Biniszkiewicz D, Lyko F, Clark V, Bird AP, and Jaenisch R (2000) Non-CpG methylation is prevalent in embryonic stem cells and may be mediated by DNA methyltransferase 3a. *Proc Natl Acad Sci U S A* 97: 5237-5242.
41. Lister R, Pelizzola M, Dowen RH, Hawkins RD, Hon G, Tonti-Filippini J, et al. (2009) Human DNA methylomes at base resolution show widespread epigenomic differences. *Nature* 462: 315-322.
42. Kriaucionis S and Heintz N (2009) The nuclear DNA base 5-hydroxymethylcytosine is present in Purkinje neurons and the brain. *Science* 324: 929-930.
43. Tahiliani M, Koh KP, Shen Y, Pastor WA, Bandukwala H, Brudno Y, Agarwal S, Iyer LM, Liu DR, Aravind L, and Rao A (2009) Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. *Science* 324: 930-935.
44. Valinluck V, Tsai HH, Rogstad DK, Burdzy A, Bird A, and Sowers LC (2004) Oxidative damage to methyl-CpG sequences inhibits the binding of the methyl-CpG binding domain (MBD) of methyl-CpG binding protein 2 (MeCP2). *Nucleic Acids Res* 32: 4100-4108.
45. Branco MR, Ficz G, and Reik W (2012) Uncovering the role of 5-hydroxymethylcytosine in the epigenome. *Nat Rev Genet* 13: 7-13.
46. Globisch D, Munzel M, Muller M, Michalakis S, Wagner M, Koch S, Bruckl T, Biel M, and Carell T (2010) Tissue distribution of 5-hydroxymethylcytosine and search for active demethylation intermediates. *PLoS ONE* 5: e15367.
47. Dunham I, Kundaje A, Aldred SF, Collins PJ, Davis CA, Doyle F, et al. (2012) An integrated encyclopedia of DNA elements in the human genome. *Nature* 489: 57-74.

48. Kuehn P, Mischke M, Wiegand S, Sers C, Horsthemke B, Lau S, Keil T, Lee YA, Grueters A, and Krude H (2012) An Alu element-associated hypermethylation variant of the POMC gene is associated with childhood obesity. *PLoS Genet* 8: e1002543.
49. Toporoff G, Aran D, Kark JD, Rosenberg M, Dubnikov T, Nissan B, Wainstein J, Friedlander Y, Levy-Lahad E, Glaser B, and Hellman A (2012) Genome-wide survey reveals predisposing diabetes type 2-related DNA methylation variations in human peripheral blood. *Hum Mol Genet* 21: 371-383.
50. Issa JP (2011) Epigenetic variation and cellular Darwinism. *Nat Genet* 43: 724-726.
51. Landan G, Cohen NM, Mukamel Z, Bar A, Molchadsky A, Brosh R, et al. (2012) Epigenetic polymorphism and the stochastic formation of differentially methylated regions in normal and cancerous tissues. *Nat Genet* 44: 1207-1214.
52. Jones PA and Baylin SB (2002) The fundamental role of epigenetic events in cancer. *Nat Rev Genet* 3: 415-428.
53. Jones PA and Baylin SB (2007) The epigenomics of cancer. *Cell* 128: 683-692.
54. Baylin SB and Jones PA (2011) A decade of exploring the cancer epigenome - biological and translational implications. *Nat Rev Cancer* 11: 726-734.
55. Movassagh M, Choy MK, Goddard M, Bennett MR, Down TA, and Foo RS (2010) Differential DNA methylation correlates with differential expression of angiogenic factors in human heart failure. *PLoS ONE* 5: e8564.
56. Kaneda R, Takada S, Yamashita Y, Choi YL, Nonaka-Sarukawa M, Soda M, Misawa Y, Isomura T, Shimada K, and Mano H (2009) Genome-wide histone methylation profile for heart failure. *Genes Cells* 14: 69-77.

57. Ollikainen M and Craig JM (2011) Epigenetic discordance at imprinting control regions in twins. *Epigenomics* 3: 295-306.
58. Bell JT, Tsai PC, Yang TP, Pidsley R, Nisbet J, Glass D, et al. (2012) Epigenome-wide scans identify differentially methylated regions for age and age-related phenotypes in a healthy ageing population. *PLoS Genet* 8: e1002629.
59. Martin GM (2009) Epigenetic gambling and epigenetic drift as an antagonistic pleiotropic mechanism of aging. *Aging Cell* 8: 761-764.
60. Heijmans BT, Kremer D, Tobi EW, Boomsma DI, and Slagboom PE (2007) Heritable rather than age-related environmental and stochastic factors dominate variation in DNA methylation of the human IGF2/H19 locus. *Hum Mol Genet* 16: 547-554.
61. Gertz J, Varley KE, Reddy TE, Bowling KM, Pauli F, Parker SL, Kucera KS, Willard HF, and Myers RM (2011) Analysis of DNA methylation in a three-generation family reveals widespread genetic influence on epigenetic regulation. *PLoS Genet* 7: e1002228.
62. Ollikainen M, Smith KR, Joo EJ, Ng HK, Andronikos R, Novakovic B, bdul Aziz NK, Carlin JB, Morley R, Saffery R, and Craig JM (2010) DNA methylation analysis of multiple tissues from newborn twins reveals both genetic and intrauterine components to variation in the human neonatal epigenome. *Hum Mol Genet* 19: 4176-4188.
63. Dolinoy DC, Weidman JR, Waterland RA, and Jirtle RL (2006) Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. *Environ Health Perspect* 114: 567-572.
64. Goldberg AD, Allis CD, and Bernstein E (2007) Epigenetics: a landscape takes shape. *Cell* 128: 635-638.

65. Gluckman PD, Hanson MA, Buklijas T, Low FM, and Beedle AS (2009) Epigenetic mechanisms that underpin metabolic and cardiovascular diseases. *Nat Rev Endocrinol* 5: 401-408.
66. Attig L, Gabory A, and Junien C (2010) Early nutrition and epigenetic programming: chasing shadows. *Curr Opin Clin Nutr Metab Care* 13: 284-293.
67. Joubert BR, Haberg SE, Nilsen RM, Wang X, Vollset SE, et al. (2012) 450K epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. *Environ Health Perspect* 120: 1425-1431.
68. Jirtle RL and Skinner MK (2007) Environmental epigenomics and disease susceptibility. *Nat Rev Genet* 8: 253-262.
69. Heijmans BT, Tobi EW, Lumey LH, and Slagboom PE (2009) The epigenome: Archive of the prenatal environment. *Epigenetics* 4: 526-531.
70. Petronis A (2006) Epigenetics and twins: three variations on the theme. *Trends Genet* 22: 347-350.
71. Breitling LP, Yang R, Korn B, Burwinkel B, and Brenner H (2011) Tobacco-smoking-related differential DNA methylation: 27K discovery and replication. *Am J Hum Genet* 88: 450-457.
72. Monick MM, Beach SR, Plume J, Sears R, Gerrard M, Brody GH, and Philibert RA (2012) Coordinated changes in AHRR methylation in lymphoblasts and pulmonary macrophages from smokers. *Am J Med Genet B Neuropsychiatr Genet* 159B: 141-151.
73. Bollati V, Baccarelli A, Hou L, Bonzini M, Fustinoni S, Cavallo D, Byun HM, Jiang J, Marinelli B, Pesatori AC, Bertazzi PA, and Yang AS (2007) Changes in DNA methylation patterns in subjects exposed to low-dose benzene. *Cancer Res* 67: 876-880.

74. Ren X, McHale CM, Skibola CF, Smith AH, Smith MT, and Zhang L (2011) An emerging role for epigenetic dysregulation in arsenic toxicity and carcinogenesis. *Environ Health Perspect* 119: 11-19.
75. Suarez-Alvarez B, Baragano RA, Ortega F, and Lopez-Larrea C (2013) Epigenetic modulation of the immune function: A potential target for tolerance. *Epigenetics* 8.
76. Kubo M and Motomura Y (2012) Transcriptional regulation of the anti-inflammatory cytokine IL-10 in acquired immune cells. *Front Immunol* 3: 275.
77. Lam LL, Emberly E, Fraser HB, Neumann SM, Chen E, Miller GE, and Kobor MS (2012) Factors underlying variable DNA methylation in a human community cohort. *Proc Natl Acad Sci U S A*.
78. Harrison A and Parle-McDermott A (2011) DNA methylation: a timeline of methods and applications. *Front Genet* 2: 74.
79. Bock C, Tomazou EM, Brinkman AB, Muller F, Simmer F, Gu H, Jager N, Gnirke A, Stunnenberg HG, and Meissner A (2010) Quantitative comparison of genome-wide DNA methylation mapping technologies. *Nat Biotechnol* 28: 1106-1114.
80. Novak P, Stampfer MR, Munoz-Rodriguez JL, Garbe JC, Ehrlich M, Futscher BW, and Jensen TJ (2012) Cell-type specific DNA methylation patterns define human breast cellular identity. *PLoS ONE* 7: e52299.
81. Jin SG, Kadam S, and Pfeifer GP (2010) Examination of the specificity of DNA methylation profiling techniques towards 5-methylcytosine and 5-hydroxymethylcytosine. *Nucleic Acids Res* 38: e125.
82. Gupta R, Nagarajan A, and Wajapeyee N (2010) Advances in genome-wide DNA methylation analysis. *Biotechniques* 49: iii-ixi.

83. Heyn H, Li N, Ferreira HJ, Moran S, Pisano DG, Gomez A, et al. (2012) Distinct DNA methylomes of newborns and centenarians. *Proc Natl Acad Sci U S A* 109: 10522-10527.
84. Bibikova M, Lin Z, Zhou L, Chudin E, Garcia EW, Wu B, et al. (2006) High-throughput DNA methylation profiling using universal bead arrays. *Genome Res* 16: 383-393.
85. Sandoval J, Heyn HA, Moran S, Serra-Musach J, Pujana MA, Bibikova M, and Esteller M (2011) Validation of a DNA methylation microarray for 450,000 CpG sites in the human genome. *Epigenetics* 6: 692-702.
86. Colella S, Shen L, Baggerly KA, Issa JP, and Krahe R (2003) Sensitive and quantitative universal Pyrosequencing methylation analysis of CpG sites. *Biotechniques* 35: 146-150.
87. Ehrlich M, Nelson MR, Stanssens P, Zabeau M, Liloglou T, Xinarianos G, Cantor CR, Field JK, and van den Boom D (2005) Quantitative high-throughput analysis of DNA methylation patterns by base-specific cleavage and mass spectrometry. *Proc Natl Acad Sci U S A* 102: 15785-15790.
88. Meissner A, Mikkelsen TS, Gu H, Wernig M, Hanna J, Sivachenko A, et al. (2008) Genome-scale DNA methylation maps of pluripotent and differentiated cells. *Nature* 454: 766-770.
89. Ernst J, Kheradpour P, Mikkelsen TS, Shoresh N, Ward LD, Epstein CB, et al. (2011) Mapping and analysis of chromatin state dynamics in nine human cell types. *Nature* 473: 43-49.
90. Bock C, Walter J, Paulsen M, and Lengauer T (2008) Inter-individual variation of DNA methylation and its implications for large-scale epigenome mapping. *Nucleic Acids Res* 36: e55.

91. McDaniell R, Lee BK, Song L, Liu Z, Boyle AP, Erdos MR, et al. (2010) Heritable individual-specific and allele-specific chromatin signatures in humans. *Science* 328: 235-239.
92. Bell JT, Pai AA, Pickrell JK, Gaffney DJ, Pique-Regi R, Degner JF, Gilad Y, and Pritchard JK (2011) DNA methylation patterns associate with genetic and gene expression variation in HapMap cell lines. *Genome Biol* 12: R10.
93. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, and Meaney MJ (2004) Epigenetic programming by maternal behavior. *Nat Neurosci* 7: 847-854.
94. Rakyan VK, Down TA, Balding DJ, and Beck S (2011) Epigenome-wide association studies for common human diseases. *Nat Rev Genet* 12: 529-541.
95. Xie H, Wang M, de Andrade A, Bonaldo MD, Galat V, Arndt K, Rajaram V, Goldman S, Tomita T, and Soares MB (2011) Genome-wide quantitative assessment of variation in DNA methylation patterns. *Nucleic Acids Res* .
96. Jones PA, Archer TK, Baylin SB, Beck S, Berger S, Bernstein BE, et al. (2008) Moving AHEAD with an international human epigenome project. *Nature* 454: 711-715.
97. Bernstein BE, Stamatoyannopoulos JA, Costello JF, Ren B, Milosavljevic A, Meissner A, et al. (2010) The NIH Roadmap Epigenomics Mapping Consortium. *Nat Biotechnol* 28: 1045-1048.
98. Foley DL, Craig JM, Morley R, Olsson CJ, Dwyer T, Smith K, and Saffery R (2009) Prospects for epigenetic epidemiology. *Am J Epidemiol* 169: 389-400.
99. Relton CL and Davey SG (2010) Epigenetic epidemiology of common complex disease: prospects for prediction, prevention, and treatment. *PLoS Med* 7: e1000356.

100. Byun HM, Siegmund KD, Pan F, Weisenberger DJ, Kanel G, Laird PW, and Yang AS (2009) Epigenetic profiling of somatic tissues from human autopsy specimens identifies tissue- and individual-specific DNA methylation patterns. *Hum Mol Genet* 18: 4808-4817.
101. Song F, Smith JF, Kimura MT, Morrow AD, Matsuyama T, Nagase H, and Held WA (2005) Association of tissue-specific differentially methylated regions (TDMs) with differential gene expression. *Proc Natl Acad Sci U S A* 102: 3336-3341.
102. Illingworth R, Kerr A, Desousa D, Jorgensen H, Ellis P, Stalker J, et al. (2008) A novel CpG island set identifies tissue-specific methylation at developmental gene loci. *PLoS Biol* 6: e22.
103. Martin GM (2005) Epigenetic drift in aging identical twins. *Proc Natl Acad Sci U S A* 102: 10413-10414.
104. Houseman EA, Accomando WP, Koestler DC, Christensen BC, Marsit CJ, Nelson HH, Wiencke JK, and Kelsey KT (2012) DNA methylation arrays as surrogate measures of cell mixture distribution. *BMC Bioinformatics* 13: 86.
105. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, Turecki G, and Meaney MJ (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 12: 342-348.
106. Hoyo C, Murphy SK, and Jirtle RL (2009) Imprint regulatory elements as epigenetic biosensors of exposure in epidemiological studies. *J Epidemiol Community Health* 63: 683-684.
107. Freeman B, Smith N, Curtis C, Huckett L, Mill J, and Craig IW (2003) DNA from buccal swabs recruited by mail: evaluation of storage effects on long-term stability and suitability for multiplex polymerase chain reaction genotyping. *Behav Genet* 33: 67-72.

108. Gronniger E, Weber B, Heil O, Peters N, Stab F, Wenck H, Korn B, Winnefeld M, and Lyko F (2010) Aging and chronic sun exposure cause distinct epigenetic changes in human skin. *PLoS Genet* 6: e1000971.
109. Noer A, Sorensen AL, Boquest AC, and Collas P (2006) Stable CpG hypomethylation of adipogenic promoters in freshly isolated, cultured, and differentiated mesenchymal stem cells from adipose tissue. *Mol Biol Cell* 17: 3543-3556.
110. Ronn T, Poulsen P, Hansson O, Holmkvist J, Almgren P, Nilsson P, Tuomi T, Isomaa B, Groop L, Vaag A, and Ling C (2008) Age influences DNA methylation and gene expression of COX7A1 in human skeletal muscle. *Diabetologia* 51: 1159-1168.
111. Murphy SK, Huang Z, and Hoyo C (2012) Differentially methylated regions of imprinted genes in prenatal, perinatal and postnatal human tissues. *PLoS ONE* 7: e40924.
112. Mill J and Heijmans BT (2013) From promises to practical strategies in epigenetic epidemiology. *Nat Rev Genet* 14: 585-594.
113. Boomsma DI, de Geus EJ, Vink JM, Stubbe JH, Distel MA, Hottenga JJ, Posthuma D, van Beijsterveldt TC, Hudziak JJ, Bartels M, and Willemsen G (2006) Netherlands Twin Register: from twins to twin families. *Twin Res Hum Genet* 9: 849-857.
114. Boomsma DI, Willemsen G, Sullivan PF, Heutink P, Meijer P, et al. (2008) Genome-wide association of major depression: description of samples for the GAIN Major Depressive Disorder Study: NTR and NESDA biobank projects. *Eur J Hum Genet* 16: 335-342.
115. Wang L, Wang F, Guan J, Le J, Wu L, Zou J, Zhao H, Pei L, Zheng X, and Zhang T (2010) Relation between hypomethylation of long interspersed nucleotide elements and risk of neural tube defects. *Am J Clin Nutr* 91: 1359-1367.

116. Willemse G, de Geus EJ, Bartels M, van Beijsterveldt CE, Brooks AI, Estourgie-van Burk GF, et al. (2010) The Netherlands Twin Register biobank: a resource for genetic epidemiological studies. *Twin Res Hum Genet* 13: 231-245.
117. McGue M and Christensen K (2007) Social activity and healthy aging: a study of aging Danish twins. *Twin Res Hum Genet* 10: 255-265.
118. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, et al. (1999) The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. *Am J Cardiol* 84: 1192-1197.
119. Waterland RA and Michels KB (2007) Epigenetic Epidemiology of the Developmental Origins Hypothesis. *Annu Rev Nutr* .
120. Steegers-Theunissen RP, Obermann-Borst SA, Kremer D, Lindemans J, Siebel C, Steegers EA, Slagboom PE, and Heijmans BT (2009) Periconceptional maternal folic acid use of 400 µg per day is related to increased methylation of the IGF2 gene in the very young child. *PLoS ONE* 4: e7845.
121. Kouzarides T (2007) SnapShot: Histone-modifying enzymes. *Cell* 128: 802-U27.
122. Petronis A (2001) Human morbid genetics revisited: relevance of epigenetics. *Trends Genet* 17: 142-146.
123. Pons D, de Vries FR, van den Elsen PJ, Heijmans BT, Quax PH, and Jukema JW (2009) Epigenetic histone acetylation modifiers in vascular remodelling: new targets for therapy in cardiovascular disease. *Eur Heart J* 30: 266-277.
124. Turunen MP, Aavik E, and Yla-Herttuala S (2009) Epigenetics and atherosclerosis. *Biochim Biophys Acta* .

125. Shen L and Waterland RA (2007) Methods of DNA methylation analysis. *Curr Opin Clin Nutr Metab Care* 10: 576-581.
126. Smith ZD, Gu H, Bock C, Gnirke A, and Meissner A (2009) High-throughput bisulfite sequencing in mammalian genomes. *Methods* 48: 226-232.
127. Rakyan VK, Hildmann T, Novik KL, Lewin J, Tost J, Cox AV, et al. (2004) DNA methylation profiling of the human major histocompatibility complex: a pilot study for the human epigenome project. *PLoS Biol* 2: e405.
128. Waterland RA and Jirtle RL (2003) Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol* 23: 5293-5300.
129. Irizarry RA, Ladd-Acosta C, Wen B, Wu Z, Montano C, Onyango P, et al. (2009) The human colon cancer methylome shows similar hypo- and hypermethylation at conserved tissue-specific CpG island shores. *Nat Genet* 41: 178-186.
130. Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, et al. (2005) Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci U S A* 102: 10604-10609.
131. Bjornsson HT, Sigurdsson MI, Fallin MD, Irizarry RA, Aspelund T, Cui H, et al. (2008) Intra-individual change over time in DNA methylation with familial clustering. *JAMA* 299: 2877-2883.
132. Ito Y, Koessler T, Ibrahim AE, Rai S, Vowler SL, bu-Amero S, et al. (2008) Somatically acquired hypomethylation of IGF2 in breast and colorectal cancer. *Hum Mol Genet* 17: 2633-2643.
133. Cui H, Cruz-Correa M, Giardiello FM, Hutcheon DF, Kafonek DR, Brandenburg S, Wu Y, He X, Powe NR, and Feinberg AP (2003) Loss of IGF2 imprinting: a potential marker of colorectal cancer risk. *Science* 299: 1753-1755.

134. Ally MS, Al-Ghafari R, and Pufulete M (2009) The relationship between gene-specific DNA methylation in leukocytes and normal colorectal mucosa in subjects with and without colorectal tumors. *Cancer Epidemiol Biomarkers Prev* 18: 922-928.
135. Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, Slagboom PE, and Heijmans BT (2009) DNA Methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Hum Mol Genet* 18: 4046-4053.
136. Dong J, Ivascu C, Chang HD, Wu P, Angeli R, Maggi L, et al. (2007) IL-10 Is Excluded from the Functional Cytokine Memory of Human CD4+ Memory T Lymphocytes. *J Immunol* 179: 2389-2396.
137. Hayward BE, Kamiya M, Strain L, Moran V, Campbell R, Hayashizaki Y, and Bonthron DT (1998) The human GNAS1 gene is imprinted and encodes distinct paternally and biallelically expressed G proteins. *Proc Natl Acad Sci U S A* 95: 10038-10043.
138. Sullivan KE, Reddy AB, Dietzmann K, Suriano AR, Kocieda VP, Stewart M, and Bhatia M (2007) Epigenetic regulation of tumor necrosis factor alpha. *Mol Cell Biol* 27: 5147-5160.
139. Sandovici I, Leppert M, Hawk PR, Suarez A, Linares Y, and Sapienza C (2003) Familial aggregation of abnormal methylation of parental alleles at the IGF2/H19 and IGF2R differentially methylated regions. *Hum Mol Genet* 12: 1569-1578.
140. Arnaud P, Monk D, Hitchins M, Gordon E, Dean W, Beechey CV, Peters J, Craigen W, Preece M, Stanier P, Moore GE, and Kelsey G (2003) Conserved methylation imprints in the human and mouse GRB10 genes with divergent allelic expression suggests differential reading of the same mark. *Hum Mol Genet* 12: 1005-1019.

141. Melzner I, Scott V, Dorsch K, Fischer P, Wabitsch M, Bruderlein S, Hasel C, and Moller P (2002) Leptin gene expression in human preadipocytes is switched on by maturation-induced demethylation of distinct CpGs in its proximal promoter. *J Biol Chem* 277: 45420-45427.
142. McGill BE, Bundle SF, Yaylaoglu MB, Carson JP, Thaller C, and Zoghbi HY (2006) Enhanced anxiety and stress-induced corticosterone release are associated with increased Crh expression in a mouse model of Rett syndrome. *Proc Natl Acad Sci U S A* 103: 18267-18272.
143. Probst MC, Thumann H, Aslanidis C, Langmann T, Buechler C, Patsch W, Baralle FE, linga-Thie GM, Geisel J, Keller C, Menys VC, and Schmitz G (2004) Screening for functional sequence variations and mutations in ABCA1. *Atherosclerosis* 175: 269-279.
144. Adkins RM, Fain JN, Krushkal J, Klauser CK, Magann EF, and Morrison JC (2007) Association between paternally inherited haplotypes upstream of the insulin gene and umbilical cord IGF-II levels. *Pediatr Res* 62: 451-455.
145. Mitsuya K, Meguro M, Lee MP, Katoh M, Schulz TC, Kugoh H, Yoshida MA, Niikawa N, Feinberg AP, and Oshimura M (1999) LIT1, an imprinted antisense RNA in the human KvLQT1 locus identified by screening for differentially expressed transcripts using monochromosomal hybrids. *Hum Mol Genet* 8: 1209-1217.
146. Rosa AL, Wu YQ, Kwabi-Addo B, Coveler KJ, Sutton VR, and Shaffer LG (2005) Allele-specific methylation of a functional CTCF binding site upstream of MEG3 in the human imprinted domain of 14q32. *Chromosome Res* 13: 809-818.

147. Medstrand P, Landry JR, and Mager DL (2001) Long terminal repeats are used as alternative promoters for the endothelin B receptor and apolipoprotein C-I genes in humans. *J Biol Chem* 276: 1896-1903.
148. Hayward BE and Bontron DT (2000) An imprinted antisense transcript at the human GNAS1 locus. *Hum Mol Genet* 9: 835-841.
149. Li LC and Dahiya R (2002) MethPrimer: designing primers for methylation PCRs. *Bioinformatics* 18: 1427-1431.
150. Kent WJ, Sugnet CW, Furey TS, Roskin KM, Pringle TH, Zahler AM, and Haussler D (2002) The human genome browser at UCSC. *Genome Res* 12: 996-1006.
151. Coolen MW, Statham AL, Gardiner-Garden M, and Clark SJ (2007) Genomic profiling of CpG methylation and allelic specificity using quantitative high-throughput mass spectrometry: critical evaluation and improvements. *Nucleic Acids Res* 35: e119.
152. Ehrich M, Turner J, Gibbs P, Lipton L, Giovannetti M, Cantor C, and van den Boom D (2008) Cytosine methylation profiling of cancer cell lines. *Proc Natl Acad Sci U S A* 105: 4844-4849.
153. Thompson RF, Suzuki M, Lau KW, and Greally JM (2009) A pipeline for the quantitative analysis of CG dinucleotide methylation using mass spectrometry. *Bioinformatics* 25: 2164-2170.
154. Stanssens P, Zabeau M, Meersseman G, Remes G, Gansemans Y, Storm N, Hartmer R, Honisch C, Rodi CP, Bocker S, and van den Boom D (2004) High-throughput MALDI-TOF discovery of genomic sequence polymorphisms. *Genome Res* 14: 126-133.
155. Altman DG (1991) Practical statistics for medical research. London; New York: Chapman and Hall.

156. West B, Welch K, and Galecki A (12-1-2006) Linear Mixed Models: A Practical Guide Using Statistical Software. Chapman Hall / CRC Press.
157. El-Maarri O, Becker T, Junen J, Manzoor SS, az-Lacava A, Schwaab R, Wienker T, and Oldenburg J (2007) Gender specific differences in levels of DNA methylation at selected loci from human total blood: a tendency toward higher methylation levels in males. *Hum Genet* 122: 505-514.
158. Herman JG, Graff JR, Myohanen S, Nelkin BD, and Baylin SB (1996) Methylation-specific PCR: a novel PCR assay for methylation status of CpG islands. *Proc Natl Acad Sci U S A* 93: 9821-9826.
159. The International HapMap Consortium (2003) The International HapMap Project. *Nature* 426: 789-796.
160. Bourc'his D, Xu GL, Lin CS, Bollman B, and Bestor TH (2001) Dnmt3L and the establishment of maternal genomic imprints. *Science* 294: 2536-2539.
161. Ooi SK, Qiu C, Bernstein E, Li K, Jia D, Yang Z, Erdjument-Bromage H, Tempst P, Lin SP, Allis CD, Cheng X, and Bestor TH (2007) DNMT3L connects unmethylated lysine 4 of histone H3 to de novo methylation of DNA. *Nature* 448: 714-717.
162. Ramchandani S, Bhattacharya SK, Cervoni N, and Szyf M (1999) DNA methylation is a reversible biological signal. *Proc Natl Acad Sci U S A* 96: 6107-6112.
163. Bollati V, Schwartz J, Wright R, Litonjua A, Tarantini L, Suh H, Sparrow D, Vokonas P, and Baccarelli A (2009) Decline in genomic DNA methylation through aging in a cohort of elderly subjects. *Mech Ageing Dev* 130: 234-239.
164. Hales CN and Barker DJ (2001) The thrifty phenotype hypothesis. *Br Med Bull* 60: 5-20.

165. Barker DJ (2007) The origins of the developmental origins theory. *J Intern Med* 261: 412-417.
166. Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, et al. (2008) Birth weight and risk of type 2 diabetes: a systematic review. *JAMA* 300: 2886-2897.
167. Lumey LH, Stein AD, Kahn HS, and Romijn JA (2009) Lipid profiles in middle-aged men and women after famine exposure during gestation: the Dutch Hunger Winter Families Study. *Am J Clin Nutr* 89: 1737-1743.
168. Roseboom TJ, de Rooij S, and Painter R (2006) The Dutch famine and its long-term consequences for adult health. *Early Hum Dev* 82: 485-491.
169. Stein AD, Kahn HS, Rundle A, Zybert PA, van der Pal-de Bruin, and Lumey LH (2007) Anthropometric measures in middle age after exposure to famine during gestation: evidence from the Dutch famine. *Am J Clin Nutr* 85: 869-876.
170. Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D, and Gorman JM (1996) Schizophrenia after prenatal famine. Further evidence. *Arch Gen Psychiatry* 53: 25-31.
171. Kyle UG and Pichard C (2006) The Dutch Famine of 1944-1945: a pathophysiological model of long-term consequences of wasting disease. *Curr Opin Clin Nutr Metab Care* 9: 388-394.
172. Brown AS and Susser ES (1997) Sex differences in prevalence of congenital neural defects after periconceptional famine exposure. *Epidemiology* 8: 55-58.
173. Ravelli AC, van der Meulen JH, Osmond C, Barker DJ, and Bleker OP (1999) Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am J Clin Nutr* 70: 811-816.

174. Bygren LO, Edvinsson S, and Brostrom G (2000) Change in food availability during pregnancy: Is it related to adult sudden death from cerebro- and cardiovascular disease in offspring? *Am J Hum Biol* 12: 447-453.
175. Painter RC, de Rooij S, Bossuyt PM, Simmers TA, Osmond C, Barker DJ, Bleker OP, and Roseboom TJ (2006) Early onset of coronary artery disease after prenatal exposure to the Dutch famine. *Am J Clin Nutr* 84: 322-327.
176. Gilbert JS and Nijland MJ (2008) Sex differences in the developmental origins of hypertension and cardiorenal disease. *Am J Physiol Regul Integr Comp Physiol* 295: R1941-R1952.
177. Nathanielsz PW (2006) Animal models that elucidate basic principles of the developmental origins of adult diseases. *ILAR J* 47: 73-82.
178. Gluckman PD, Hanson MA, Cooper C, and Thornburg KL (2008) Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 359: 61-73.
179. Waterland RA, Dolinoy DC, Lin JR, Smith CA, Shi X, and Tahiliani KG (2006) Maternal methyl supplements increase offspring DNA methylation at Axin Fused. *Genesis* 44: 401-406.
180. Monk D, Sanches R, Arnaud P, Apostolidou S, Hills FA, bu-Amero S, Murrell A, Friess H, Reik W, Stanier P, Constancia M, and Moore GE (2006) Imprinting of IGF2 P0 transcript and novel alternatively spliced INS-IGF2 isoforms show differences between mouse and human. *Hum Mol Genet* 15: 1259-1269.
181. Morgan HD, Santos F, Green K, Dean W, and Reik W (2005) Epigenetic reprogramming in mammals. *Hum Mol Genet* 14 Spec No 1: R47-R58.
182. Reik W, Dean W, and Walter J (2001) Epigenetic reprogramming in mammalian development. *Science* 293: 1089-1093.

183. Morgan HD, Jin XL, Li A, Whitelaw E, and O'Neill C (2008) The culture of zygotes to the blastocyst stage changes the postnatal expression of an epigenetically labile allele, agouti viable yellow, in mice. *Biol Reprod* 79: 618-623.
184. Sinclair KD, Allegrucci C, Singh R, Gardner DS, Sebastian S, Bispham J, et al. (2007) DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptional B vitamin and methionine status. *Proc Natl Acad Sci U S A* 104: 19351-19356.
185. Yamagata Y, Asada H, Tamura I, Lee L, Maekawa R, Taniguchi K, Taketani T, Matsuoka A, Tamura H, and Sugino N (2009) DNA methyltransferase expression in the human endometrium: down-regulation by progesterone and estrogen. *Hum Reprod* 24: 1126-1132.
186. Bjornsson HT, Fallin MD, and Feinberg AP (2004) An integrated epigenetic and genetic approach to common human disease. *Trends Genet* 20: 350-358.
187. Duijts L, Bakker-Jonges LE, Labout JA, Jaddoe VW, Hofman A, Steegers EA, van Dongen JJ, Hooijkaas H, and Moll HA (2009) Fetal growth influences lymphocyte subset counts at birth: the Generation R Study. *Neonatology* 95: 149-156.
188. Lillycrop KA, Phillips ES, Torrens C, Hanson MA, Jackson AA, and Burdge GC (2008) Feeding pregnant rats a protein-restricted diet persistently alters the methylation of specific cytosines in the hepatic PPAR alpha promoter of the offspring. *Br J Nutr* 100: 278-282.
189. Stöger R (2008) The thrifty epigenotype: an acquired and heritable predisposition for obesity and diabetes? *Bioessays* 30: 156-166.

190. Prentice AM, Rayco-Solon P, and Moore SE (2005) Insights from the developing world: thrifty genotypes and thrifty phenotypes. *Proc Nutr Soc* 64: 153-161.
191. Stoger R (2006) In vivo methylation patterns of the leptin promoter in human and mouse. *Epigenetics* 1: 155-162.
192. Bocchio CL, Boin F, Zanardini R, Popoli M, Michelato A, Bignotti S, Tura GB, and Gennarelli M (2002) Association between promoter polymorphic haplotypes of interleukin-10 gene and schizophrenia. *Biol Psychiatry* 51: 480-484.
193. Ozbey U, Tug E, and Namli M (2009) Interleukin-10 gene promoter polymorphism in patients with schizophrenia in a region of East Turkey. *World J Biol Psychiatry* 10: 461-468.
194. Burger GCE, Drummond JC, and Sandstead HR (1948) Malnutrition and Starvation in Western Netherlands, September 1944-July 1945. The Hague: General State Printing Office.
195. Talens RP, Boomsma DI, Tobi EW, Kremer D, Jukema JW, Willemse G, Putter H, Slagboom PE, and Heijmans BT (2010) Variation, patterns, and temporal stability of DNA methylation: considerations for epigenetic epidemiology. *FASEB J* 24: 3135-3144.
196. Eckhardt F, Lewin J, Cortese R, Rakyan VK, Attwood J, Burger M, et al. (2006) DNA methylation profiling of human chromosomes 6, 20 and 22. *Nat Genet* 38: 1378-1385.
197. Feinberg AP, Irizarry RA, Fradin D, Aryee MJ, Murakami P, Aspelund T, Eiriksdottir G, Harris TB, Launer L, Gudnason V, and Fallin MD (2010) Personalized epigenomic signatures that are stable over time and covary with body mass index. *Sci Transl Med* 2: 49ra67.

198. Bell JT, and Spector TD (2011) A twin approach to unraveling epigenetics. *Trends Genet* 27: 116-125.
199. Martin N, Boomsma D, and Machin G (1997) A twin-pronged attack on complex traits. *Nat Genet* 17: 387-392.
200. Kuroda A, Rauch TA, Todorov I, Ku HT, Al-Abdullah IH, Kandeel F, Mullen Y, Pfeifer GP, and Ferreri K (2009) Insulin gene expression is regulated by DNA methylation. *PLoS ONE* 4: e6953.
201. Williamson CM, Turner MD, Ball ST, Nottingham WT, Glenister P, Fray M, et al. (2006) Identification of an imprinting control region affecting the expression of all transcripts in the Gnas cluster. *Nat Genet* 38: 350-355.
202. Heijmans BT and Mill J (2012) Commentary: The seven plagues of epigenetic epidemiology. *Int J Epidemiol* 41: 74-78.
203. Purcell S (2002) Variance components models for gene-environment interaction in twin analysis. *Twin Res* 5: 554-571.
204. Wong CC, Caspi A, Williams B, Craig IW, Houts R, Ambler A, Moffitt TE, and Mill J (2010) A longitudinal study of epigenetic variation in twins. *Epigenetics* 5: 516-526.
205. Thompson RF, Atzman G, Gheorghe C, Liang HQ, Lowes C, Greally JM, and Barzilai N (2010) Tissue-specific dysregulation of DNA methylation in aging. *Aging Cell* 9: 506-518.
206. McEvoy BP, Montgomery GW, McRae AF, Ripatti S, Perola M, et al. (2009) Geographical structure and differential natural selection among North European populations. *Genome Res* 19: 804-814.

207. Christensen K, Bathum L, and Christiansen L (2008) Biological Indicators and Genetic Information in Danish Twin and Oldest-old Surveys. In: Weinstein M, Vaupel JW, Wachter KW, editors. *Biosocial Surveys*. Washington: The National Academies Press. pp. 15-41.
208. Skytthe A, Kyvik K, Bathum L, Holm N, Vaupel JW, and Christensen K (2006) The Danish Twin Registry in the new millennium. *Twin Res Hum Genet* 9: 763-771.
209. Gluckman PD and Hanson MA (2004) Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. *Pediatr Res* 56: 311-317.
210. Barker DJ (1995) The Wellcome Foundation Lecture, 1994. The fetal origins of adult disease. *Proc Biol Sci* 262: 37-43.
211. de Rooij S, Painter RC, Roseboom TJ, Phillips DI, Osmond C, Barker DJ, Tanck MW, Michels RP, Bossuyt PM, and Bleker OP (2006) Glucose tolerance at age 58 and the decline of glucose tolerance in comparison with age 50 in people prenatally exposed to the Dutch famine. *Diabetologia* 49: 637-643.
212. Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, and Burdge GC (2005) Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. *J Nutr* 135: 1382-1386.
213. Gluckman PD, Lillycrop KA, Vickers MH, Pleasants AB, Phillips ES, Beedle AS, Burdge GC, and Hanson MA (2007) Metabolic plasticity during mammalian development is directionally dependent on early nutritional status. *Proc Natl Acad Sci U S A* 104: 12796-12800.
214. Rakyan VK, Blewitt ME, Druker R, Preis JI, and Whitelaw E (2002) Metastable epialleles in mammals. *Trends Genet* 18: 348-351.

215. Einstein F, Thompson RF, Bhagat TD, Fazzari MJ, Verma A, Barzilai N, and Greally JM (2010) Cytosine methylation dysregulation in neonates following intrauterine growth restriction. PLoS ONE 5: e8887.
216. Breton CV, Byun HM, Wenten M, Pan F, Yang A, and Gilliland FD (2009) Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. Am J Respir Crit Care Med 180: 462-467.
217. Thornburg KL, O'Tierney PF, and Louey S (2010) Review: The placenta is a programming agent for cardiovascular disease. Placenta 31 Suppl: S54-S59.
218. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. (2002) Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 360: 1623-1630.
219. Hoyo C, Murtha AP, Schildkraut JM, Jirtle RL, mark-Wahnefried W, Forman MR, Iversen ES, Kurtzberg J, Overcash F, Huang Z, and Murphy SK (2011) Methylation variation at IGF2 differentially methylated regions and maternal folic acid use before and during pregnancy. Epigenetics 6: 928-936.
220. Kim M, Long TI, Arakawa K, Wang R, Yu MC, and Laird PW (2010) DNA methylation as a biomarker for cardiovascular disease risk. PLoS ONE 5: e9692.
221. Baccarelli A, Wright R, Bollati V, Litonjua A, Zanobetti A, Tarantini L, Sparrow D, Vokonas P, and Schwartz J (2010) Ischemic heart disease and stroke in relation to blood DNA methylation. Epidemiology 21: 819-828.
222. Barker DJ, Osmond C, Forsen TJ, Kajantie E, and Eriksson JG (2005) Trajectories of growth among children who have coronary events as adults. N Engl J Med 353: 1802-1809.

223. Weinstein LS, Xie T, Zhang QH, and Chen M (2007) Studies of the regulation and function of the G(s) alpha gene Gnas using gene targeting technology. *Pharmacol Ther* 115: 271-291.
224. Moore GE, bu-Amero SN, Bell G, Wakeling EL, Kingsnorth A, Stanier P, Jauniaux E, and Bennett ST (2001) Evidence that insulin is imprinted in the human yolk sac. *Diabetes* 50: 199-203.
225. Christian P and Stewart CP (2010) Maternal micronutrient deficiency, fetal development, and the risk of chronic disease. *J Nutr* 140: 437-445.
226. Power C, Atherton K, and Thomas C (2010) Maternal smoking in pregnancy, adult adiposity and other risk factors for cardiovascular disease. *Atherosclerosis* 211: 643-648.
227. Christensen BC, Houseman EA, Marsit CJ, Zheng S, Wrensch MR, Wiemels JL, et al. (2009) Aging and environmental exposures alter tissue-specific DNA methylation dependent upon CpG island context. *PLoS Genet* 5: e1000602.
228. Madsen L and Kristiansen K (2010) The importance of dietary modulation of cAMP and insulin signaling in adipose tissue and the development of obesity. *Ann N Y Acad Sci* 1190: 1-14.
229. Joakimsen O, Bonaa KH, Stensland-Bugge E, and Jacobsen BK (1999) Age and sex differences in the distribution and ultrasound morphology of carotid atherosclerosis: the Tromso Study. *Arterioscler Thromb Vasc Biol* 19: 3007-3013.
230. Theres H, Maier B, Matteucci GR, Schnippa S, Kallischnigg G, Schuren KP, and Thimme W (2004) Influence of gender on treatment and short-term mortality of patients with acute myocardial infarction in Berlin. *Z Kardiol* 93: 954-963.

231. Maekawa M and Watanabe Y (2007) Epigenetics: relations to disease and laboratory findings. *Curr Med Chem* 14: 2642-2653.
232. Liu Y, Aryee MJ, Padyukov L, Fallin MD, Hesselberg E, Runarsson A, et al. (2013) Epigenome-wide association data implicate DNA methylation as an intermediary of genetic risk in rheumatoid arthritis. *Nat Biotechnol* 31: 142-147.
233. Talens RP, Jukema JW, Trompet S, Kremer D, Westendorp RG, Lumey LH, Sattar N, Putter H, Slagboom PE, and Heijmans BT (2012) Hypermethylation at loci sensitive to the prenatal environment is associated with increased incidence of myocardial infarction. *Int J Epidemiol* 41: 106-115.
234. Davies MN, Volta M, Pidsley R, Lunnon K, Dixit A, Lovestone S, et al. (2012) Functional annotation of the human brain methylome identifies tissue-specific epigenetic variation across brain and blood. *Genome Biol* 13: R43.
235. Heijmans BT, Westendorp RG, Knook DL, Kluft C, and Slagboom PE (1999) Angiotensin I-converting enzyme and plasminogen activator inhibitor-1 gene variants: risk of mortality and fatal cardiovascular disease in an elderly population-based cohort. *J Am Coll Cardiol* 34: 1176-1183.
236. Docherty SJ, Davis OS, Haworth CM, Plomin R, and Mill J (2009) Bisulfite-based epityping on pooled genomic DNA provides an accurate estimate of average group DNA methylation. *Epigenetics Chromatin* 2: 3.
237. Du P, Kibbe WA, and Lin SM (2008) lumi: a pipeline for processing Illumina microarray. *Bioinformatics* 24: 1547-1548.
238. Wong N, Morley R, Saffery R, and Craig J (2008) Archived Guthrie blood spots as a novel source for quantitative DNA methylation analysis. *Biotechniques* 45: 423-4, 426, 428.

239. Du P, Zhang X, Huang CC, Jafari N, Kibbe WA, Hou L, and Lin SM (2010) Comparison of Beta-value and M-value methods for quantifying methylation levels by microarray analysis. *BMC Bioinformatics* 11: 587.
240. Bock C, Halachev K, Buch J, and Lengauer T (2009) EpiGRAPH: user-friendly software for statistical analysis and prediction of (epi)genomic data. *Genome Biol* 10: R14.
241. Baccarelli A, Tarantini L, Wright RO, Bollati V, Litonjua AA, Zanobetti A, Sparrow D, Vokonas P, and Schwartz J (2010) Repetitive element DNA methylation and circulating endothelial and inflammation markers in the VA normative aging study. *Epigenetics* 5.
242. Gibbs JR, van der Brug MP, Hernandez DG, Traynor BJ, Nalls MA, Lai SL, et al. (2010) Abundant quantitative trait loci exist for DNA methylation and gene expression in human brain. *PLoS Genet* 6: e1000952.
243. Tobi EW, Slagboom PE, van Dongen J, Kremer D, Stein AD, Putter H, Heijmans BT, and Lumey LH (2012) Prenatal famine and genetic variation are independently and additively associated with DNA methylation at regulatory loci within IGF2/H19. *PLoS ONE* 7: e37933.
244. Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmuhl Y, Fischer D, Holsboer F, Wotjak CT, Almeida OF, and Spengler D (2009) Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nat Neurosci* 12: 1559-1566.
245. Meulenbelt I, Droog S, Trommelen GJ, Boomsma DI, and Slagboom PE (1995) High-yield noninvasive human genomic DNA isolation method for genetic studies in geographically dispersed families and populations. *Am J Hum Genet* 57: 1252-1254.
246. Adalsteinsson BT, Gudnason H, Aspelund T, Harris TB, Launer LJ, Eiriksdottir G, Smith AV, and Gudnason V (2012) Heterogeneity in white blood

- cells has potential to confound DNA methylation measurements. PLoS ONE 7: e46705.
247. Rakyan VK, Down TA, Maslau S, Andrew T, Yang TP, Beyan H, et al. (2010) Human aging-associated DNA hypermethylation occurs preferentially at bivalent chromatin domains. Genome Res 20: 434-439.
248. Hannum G, Guinney J, Zhao L, Zhang L, Hughes G, Sadda S, et al. (2013) Genome-wide methylation profiles reveal quantitative views of human aging rates. Mol Cell 49: 359-367.
249. Teschendorff AE, West J, and Beck S (2013) Age-associated epigenetic drift: implications, and a case of epigenetic thrift? Hum Mol Genet .
250. Bocklandt S, Lin W, Sehl ME, Sanchez FJ, Sinsheimer JS, Horvath S, and Vilain E (2011) Epigenetic predictor of age. PLoS ONE 6: e14821.
251. Horvath S (2013) DNA methylation age of human tissues and cell types. Genome Biol 14: R115.
252. Zhuang J, Peng W, Li H, Wang W, Wei Y, Li W, and Xu Y (2012) Methylation of p15INK4b and expression of ANRIL on chromosome 9p21 are associated with coronary artery disease. PLoS ONE 7: e47193.
253. Visel A, Zhu Y, May D, Afzal V, Gong E, Attanasio C, Blow MJ, Cohen JC, Rubin EM, and Pennacchio LA (2010) Targeted deletion of the 9p21 non-coding coronary artery disease risk interval in mice. Nature 464: 409-412.
254. Guay SP, Brisson D, Munger J, Lamarche B, Gaudet D, and Bouchard L (2012) ABCA1 gene promoter DNA methylation is associated with HDL particle profile and coronary artery disease in familial hypercholesterolemia. Epigenetics 7: 464-472.
255. Slieker RC, Bos SD, Goeman JJ, Bovee JV, Talens RP, van der Breggen R, et al. (2013) Identification and systematic annotation of tissue-specific differentially

- methylated regions using the Illumina 450k array. *Epigenetics Chromatin* 6: 26.
256. Lowe R, Gemma C, Beyan H, Hawa MI, Bazeos A, Leslie RD, Montpetit A, Rakyan VK, and Ramagopalan SV (2013) Buccals are likely to be a more informative surrogate tissue than blood for epigenome-wide association studies. *Epigenetics* 8.
257. Smith GD (2011) Epidemiology, epigenetics and the 'Gloomy Prospect': embracing randomness in population health research and practice. *Int J Epidemiol* 40: 537-562.
258. Breitling LP, Salzmann K, Rothenbacher D, Burwinkel B, and Brenner H (2012) Smoking, F2RL3 methylation, and prognosis in stable coronary heart disease. *Eur Heart J* 33: 2841-2848.
259. Kaati G, Bygren LO, and Edvinsson S (2002) Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. *Eur J Hum Genet* 10: 682-688.
260. Kaati G, Bygren LO, Pembrey M, and Sjostrom M (2007) Transgenerational response to nutrition, early life circumstances and longevity. *Eur J Hum Genet* 15: 784-790.
261. Flusberg BA, Webster DR, Lee JH, Travers KJ, Olivares EC, Clark TA, Korlach J, and Turner SW (2010) Direct detection of DNA methylation during single-molecule, real-time sequencing. *Nat Methods* 7: 461-465.
262. Statham AL, Robinson MD, Song JZ, Coolen MW, Stirzaker C, and Clark SJ (2012) Bisulfite sequencing of chromatin immunoprecipitated DNA (BisChIP-seq) directly informs methylation status of histone-modified DNA. *Genome Res* 22: 1120-1127.
263. Lonsdale J, Thomas J, Salvatore M, Phillips R, Lo E, Shad S, et al., (2013) The Genotype-Tissue Expression (GTEx) project. *Nat Genet* 45: 580-585.

