



*The impact of folate on telomere length
and chromosome stability in
human WIL2-NS cells and lymphocytes*

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REFERENCES

1. Fenech, M. Nutritional treatment of genome instability: a paradigm shift in disease prevention and in the setting of recommended dietary allowances. *Nutrition Research Reviews* 16, 109-122 (2003).
2. Svenson, U. & Roos, G. Telomere length as a biological marker in malignancy. *Biochim Biophys Acta* 1792, 317-23 (2009).
3. Trkova, M., Kapras, J., Bobkova, K., Stankova, J. & Mejsnarova, B. Increased micronuclei frequencies in couples with reproductive failure. *Reprod Toxicol* 14, 331-5 (2000).
4. Migliore, L. *et al.* Oxidative DNA damage in peripheral leukocytes of mild cognitive impairment and AD patients. *Neurobiol Aging* 26, 567-73 (2005).
5. Migliore, L. *et al.* Chromosome and oxidative damage biomarkers in lymphocytes of Parkinson's disease patients. *Int J Hyg Environ Health* 204, 61-6 (2001).
6. Callen, E. & Surralles, J. Telomere dysfunction in genome instability syndromes. *Mutat Res* 567, 85-104 (2004).
7. Jiang, H., Ju, Z. & Rudolph, K. L. Telomere shortening and ageing. *Z Gerontol Geriatr* 40, 314-24 (2007).
8. Bonassi, S. *et al.* Chromosomal aberrations in lymphocytes predict human cancer independently of exposure to carcinogens. European Study Group on Cytogenetic Biomarkers and Health. *Cancer Res* 60, 1619-25 (2000).
9. Rossner, P. *et al.* Chromosomal aberrations in lymphocytes of healthy subjects and risk of cancer. *Environ Health Perspect* 113, 517-20 (2005).
10. Hagmar, L. *et al.* Impact of types of lymphocyte chromosomal aberrations on human cancer risk: results from Nordic and Italian cohorts. *Cancer Res* 64, 2258-63 (2004).
11. Boffetta, P. *et al.* Chromosomal aberrations and cancer risk: results of a cohort study from Central Europe. *Am J Epidemiol* 165, 36-43 (2007).
12. Fenech, M. Chromosomal biomarkers of genomic instability relevant to cancer. *Drug Discov Today* 7, 1128-37 (2002).
13. Bull, C. & Fenech, M. Genome-health nutrigenomics and nutrigenetics: nutritional requirements or 'nutriomes' for chromosomal stability and telomere maintenance at the individual level. *Proc Nutr Soc May*; 67, 146-156 (2008).
14. Fenech, M. Cytokinesis-block micronucleus cytome assay. *Nat Protoc* 2, 1084-104 (2007).
15. Lindberg, H. K. *et al.* Origin of nuclear buds and micronuclei in normal and folate-deprived human lymphocytes. *Mutat Res* 617, 33-45 (2007).

16. Bonassi, S. *et al.* An increased micronucleus frequency in peripheral blood lymphocytes predicts the risk of cancer in humans. *Carcinogenesis* 28, 625-31 (2007).
17. Murgia, E., Maggini, V., Barale, R. & Rossi, A. M. Micronuclei, genetic polymorphisms and cardiovascular disease mortality in a nested case-control study in Italy. *Mutat Res* 621, 113-8 (2007).
18. Murgia, E., Ballardin, M., Bonassi, S., Rossi, A. M. & Barale, R. Validation of micronuclei frequency in peripheral blood lymphocytes as early cancer risk biomarker in a nested case-control study. *Mutat Res* 639, 27-34 (2008).
19. Albertson, D. G. Gene amplification in cancer. *Trends Genet* 22, 447-55 (2006).
20. Stark, G. R. & Wahl, G. M. Gene amplification. *Annu Rev Biochem* 53, 447-91 (1984).
21. Miele, M., Bonatti, S., Menichini, P., Ottaggio, L. & Abbondandolo, A. The presence of amplified regions affects the stability of chromosomes in drug-resistant Chinese hamster cells. *Mutat Res* 219, 171-8 (1989).
22. Fenech, M. *et al.* HUMN project: detailed description of the scoring criteria for the cytokinesis-block micronucleus assay using isolated human lymphocyte cultures. *Mutat Res* 534, 65-75 (2003).
23. Fenech, M. The *in vitro* micronucleus technique. *Mutat Res* 455, 81-95 (2000).
24. Shimizu, N., Itoh, N., Utiyama, H. & Wahl, G. M. Selective entrapment of extrachromosomally amplified DNA by nuclear budding and micronucleation during S phase. *J Cell Biol* 140, 1307-20 (1998).
25. Shimizu, N., Shimura, T. & Tanaka, T. Selective elimination of acentric double minutes from cancer cells through the extrusion of micronuclei. *Mutat Res* 448, 81-90 (2000).
26. Barker, P. E. Double minutes in human tumor cells. *Cancer Genet Cytogenet* 5, 81-94 (1982).
27. Murnane, J. P. Telomeres and chromosome instability. *DNA Repair (Amst)* 5, 1082-92 (2006).
28. Fenech, M. & Crott, J. W. Micronuclei, nucleoplasmic bridges and nuclear buds induced in folic acid deficient human lymphocytes-evidence for breakage-fusion-bridge cycles in the cytokinesis-block micronucleus assay. *Mutat Res* 504, 131-6 (2002).
29. El-Zein, R. A. *et al.* Cytokinesis-blocked micronucleus assay as a novel biomarker for lung cancer risk. *Cancer Res* 66, 6449-56 (2006).
30. Thomas, P., Umegaki, K. & Fenech, M. Nucleoplasmic bridges are a sensitive measure of chromosome rearrangement in the cytokinesis-block micronucleus assay. *Mutagenesis* 18, 187-94 (2003).

31. Selvarajah, S. *et al.* The breakage-fusion-bridge (BFB) cycle as a mechanism for generating genetic heterogeneity in osteosarcoma. *Chromosoma* 115, 459-67 (2006).
32. Kitada, K. & Yamasaki, T. The complicated copy number alterations in chromosome 7 of a lung cancer cell line is explained by a model based on repeated breakage-fusion-bridge cycles. *Cancer Genet Cytogenet* 185, 11-9 (2008).
33. Lo, A. W. *et al.* DNA amplification by breakage/fusion/bridge cycles initiated by spontaneous telomere loss in a human cancer cell line. *Neoplasia* 4, 531-8 (2002).
34. Ames, B. N. & Wakimoto, P. Are vitamin and mineral deficiencies a major cancer risk? *Nat Rev Cancer* 2, 694-704 (2002).
35. Fenech, M. *et al.* Low intake of calcium, folate, nicotinic acid, vitamin E, retinol, beta-carotene and high intake of pantothenic acid, biotin and riboflavin are significantly associated with increased genome instability: results from a dietary intake and micronucleus index survey in South Australia. *Carcinogenesis* 26, 991-9 (2005).
36. Teo, T. & Fenech, M. The interactive effect of alcohol and folic acid on genome stability in human WIL2-NS cells measured using the cytokinesis-block micronucleus cytome assay. *Mutat Res* 657, 32-8 (2008).
37. Kimura, M., Umegaki, K., Higuchi, M., Thomas, P. & Fenech, M. Methylenetetrahydrofolate reductase C677T polymorphism, folic acid and riboflavin are important determinants of genome stability in cultured human lymphocytes. *J Nutr* 134, 48-56 (2004).
38. Wani, N. A., Hamid, A. & Kaur, J. Folate status in various pathophysiological conditions. *IUBMB Life* 60, 834-42 (2008).
39. Lightfoot, T. J. & Roman, E. Causes of childhood leukaemia and lymphoma. *Toxicol Appl Pharmacol* 199, 104-17 (2004).
40. Thomas, P., NJ, O. C. & Fenech, M. Telomere length in white blood cells, buccal cells and brain tissue and its variation with ageing and Alzheimer's disease. *Mech Ageing Dev* 129, 183-90 (2008).
41. Choi, S. W. & Mason, J. B. Folate and colorectal carcinogenesis: is DNA repair the missing link? *Am J Gastroenterol* 93, 2013-6 (1998).
42. Stolzenberg-Solomon, R. Z. *et al.* Dietary and other methyl-group availability factors and pancreatic cancer risk in a cohort of male smokers. *Am J Epidemiol* 153, 680-7 (2001).
43. Mayne, S. T. *et al.* Nutrient intake and risk of subtypes of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 10, 1055-62 (2001).
44. Thomas, P. & Fenech, M. Chromosome 17 and 21 aneuploidy in buccal cells is increased with ageing and in Alzheimer's disease. *Mutagenesis* 23, 57-65 (2008).

45. Baglietto, L., English, D. R., Gertig, D. M., Hopper, J. L. & Giles, G. G. Does dietary folate intake modify effect of alcohol consumption on breast cancer risk? Prospective cohort study. *Bmj* 331, 807 (2005).
46. Rohan, T. E., Jain, M. G., Howe, G. R. & Miller, A. B. Dietary folate consumption and breast cancer risk. *J Natl Cancer Inst* 92, 266-9 (2000).
47. Zhang, S. *et al.* A prospective study of folate intake and the risk of breast cancer. *Jama* 281, 1632-7 (1999).
48. Duffy, C. M. *et al.* Alcohol and folate intake and breast cancer risk in the WHI Observational Study. *Breast Cancer Res Treat* (2008).
49. Kabat, G. C., Miller, A. B., Jain, M. & Rohan, T. E. Dietary intake of selected B vitamins in relation to risk of major cancers in women. *Br J Cancer* 99, 816-21 (2008).
50. Smith, M. T. *et al.* Molecular biomarkers for the study of childhood leukemia. *Toxicol Appl Pharmacol* 206, 237-45 (2005).
51. Goh, Y. I., Bollano, E., Einarson, T. R. & Koren, G. Prenatal multivitamin supplementation and rates of pediatric cancers: a meta-analysis. *Clin Pharmacol Ther* 81, 685-91 (2007).
52. Lightfoot, T. J. *et al.* Risk of non-Hodgkin lymphoma associated with polymorphisms in folate-metabolizing genes. *Cancer Epidemiol Biomarkers Prev* 14, 2999-3003 (2005).
53. Thompson, J. R., Gerald, P. F., Willoughby, M. L. & Armstrong, B. K. Maternal folate supplementation in pregnancy and protection against acute lymphoblastic leukaemia in childhood: a case-control study. *Lancet* 358, 1935-40 (2001).
54. Wang, X. & Fenech, M. A comparison of folic acid and 5-methyltetrahydrofolate for prevention of DNA damage and cell death in human lymphocytes in vitro. *Mutagenesis* 18, 81-6 (2003).
55. Fenech, M. The role of folic acid and Vitamin B12 in genomic stability of human cells. *Mutat Res* 475, 57-67 (2001).
56. Ames, B. N. DNA damage from micronutrient deficiencies is likely to be a major cause of cancer. *Mutat Res* 475, 7-20 (2001).
57. Fenech, M. Genome health nutrigenomics and nutrigenetics: diagnosis and nutritional treatment of genome damage on an individual basis. *Food Chem Toxicol* 46, 1365-70 (2008).
58. Salerno, P. *et al.* [Folic acid and congenital malformation: scientific evidence and public health strategies]. *Ann Ig* 20, 519-30 (2008).

59. Canfield, M. A. *et al.* Changes in the birth prevalence of selected birth defects after grain fortification with folic acid in the United States: findings from a multi-state population-based study. *Birth Defects Res A Clin Mol Teratol* 73, 679-89 (2005).
60. Sanchez-Moreno, C., Jimenez-Escriv, A. & Martin, A. Stroke: roles of B vitamins, homocysteine and antioxidants. *Nutr Res Rev* 22, 49-67 (2009).
61. McNulty, H. & Scott, J. M. Intake and status of folate and related B-vitamins: considerations and challenges in achieving optimal status. *Br J Nutr* 99 Suppl 3, S48-54 (2008).
62. Ferguson, L. R. & Philpott, M. Nutrition and mutagenesis. *Annu Rev Nutr* 28, 313-29 (2008).
63. Shane, B. in *Folate in Health & Disease* (ed. Bailey, L. B.) 1-22 (Marcel Dekker, New York, 1995).
64. Yang, Q. *et al.* Improvement in stroke mortality in Canada and the United States, 1990 to 2002. *Circulation* 113, 1335-43 (2006).
65. Botto, L. D. *et al.* Trends of selected malformations in relation to folic acid recommendations and fortification: an international assessment. *Birth Defects Res A Clin Mol Teratol* 76, 693-705 (2006).
66. National Health & Medical Research Council (Australia) (NHMRC). Nutrient reference values for Australia and New Zealand (Including Recommended Dietary Intakes). (2006).
67. Hough, C. D., Cho, K. R., Zonderman, A. B., Schwartz, D. R. & Morin, P. J. Coordinately up-regulated genes in ovarian cancer. *Cancer Res* 61, 3869-76 (2001).
68. Mendelsohn, L. G. *et al.* The role of dietary folate in modulation of folate receptor expression, folylpolyglutamate synthetase activity and the efficacy and toxicity of lometrexol. *Adv Enzyme Regul* 36, 365-81 (1996).
69. Sauer, J., Mason, J. B. & Choi, S. W. Too much folate: a risk factor for cancer and cardiovascular disease? *Curr Opin Clin Nutr Metab Care* 12, 30-6 (2009).
70. Selhub, J. R. and Rosenberg, I.H. in *Present knowledge in nutrition*. (ed. Giegler, E. E. a. Filer, Jr, L.J.) 206-19 (ILSI Press, Washington DC, 1996).
71. Wagner, C. in *Folate in Health & Disease* (ed. Bailey, L. B.) 23-42 (Marcel Dekker, New York, 1995).
72. Fenech, M. Micronucleus frequency in human lymphocytes is related to plasma vitamin B12 and homocysteine. *Mutat Res* 428, 299-304 (1999).
73. Fenech, M. Folate and cancer initiation. Will folate fortification help to prevent genetic events that could initiate cancer? *Australian Journal of Nutrition and Dietetics* 53 Supplement, S13-S17 (1996).

74. Blount, B. C. *et al.* Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: implications for cancer and neuronal damage. *Proc Natl Acad Sci U S A* 94, 3290-5 (1997).
75. Dianov, G. L. *et al.* Repair of uracil residues closely spaced on the opposite strands of plasmid DNA results in double-strand break and deletion formation. *Mol Gen Genet* 225, 448-52 (1991).
76. Fenech, M., Aitken, C. & Rinaldi, J. Folate, vitamin B12, homocysteine status and DNA damage in young Australian adults. *Carcinogenesis* 19, 1163-71 (1998).
77. Crott, J. & Fenech, M. Preliminary study of the genotoxic potential of homocysteine in human lymphocytes in vitro. *Mutagenesis* 16, 213-7 (2001).
78. Shammas, N. W. *et al.* Elevated levels of homocysteine predict cardiovascular death, nonfatal myocardial infarction, and symptomatic bypass graft disease at 2-year follow-up following coronary artery bypass surgery. *Prev Cardiol* 11, 95-9 (2008).
79. Kesler, A. *et al.* Comparative analysis of homocysteine concentrations in patients with retinal vein occlusion versus thrombotic and atherosclerotic disorders. *Blood Coagul Fibrinolysis* 19, 259-62 (2008).
80. Mills, J. L. *et al.* Homocysteine and neural tube defects. *J Nutr* 126, 756S-760S (1996).
81. van der Put, N. M. *et al.* Altered folate and vitamin B12 metabolism in families with spina bifida offspring. *Qjm* 90, 505-10 (1997).
82. Refsum, H. *et al.* The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. *J Nutr* 136, 1731S-1740S (2006).
83. Folstein, M. *et al.* The homocysteine hypothesis of depression. *Am J Psychiatry* 164, 861-7 (2007).
84. Dias, V. V., Brissos, S., Cardoso, C., Andreazza, A. C. & Kapczinski, F. Serum homocysteine levels and cognitive functioning in euthymic bipolar patients. *J Affect Disord* (2008).
85. Clarke, R. *et al.* Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. *Arch Neurol* 55, 1449-55 (1998).
86. Dangour, A. D. *et al.* Plasma homocysteine, but not folate or vitamin B-12, predicts mortality in older people in the United Kingdom. *J Nutr* 138, 1121-8 (2008).
87. Xu, D., Neville, R. & Finkel, T. Homocysteine accelerates endothelial cell senescence. *FEBS Lett* 470, 20-4 (2000).
88. Nitenberg, A. [Hypertension, endothelial dysfunction and cardiovascular risk]. *Arch Mal Coeur Vaiss* 99, 915-21 (2006).

89. Chen, Y. H., Lin, S. J., Chen, Y. L., Liu, P. L. & Chen, J. W. Anti-inflammatory effects of different drugs/agents with antioxidant property on endothelial expression of adhesion molecules. *Cardiovasc Hematol Disord Drug Targets* 6, 279-304 (2006).
90. DeVos, L. *et al.* Associations between single nucleotide polymorphisms in folate uptake and metabolizing genes with blood folate, homocysteine, and DNA uracil concentrations. *Am J Clin Nutr* 88, 1149-58 (2008).
91. Crott, J. W., Mashiyama, S. T., Ames, B. N. & Fenech, M. F. Methylenetetrahydrofolate reductase C677T polymorphism does not alter folic acid deficiency-induced uracil incorporation into primary human lymphocyte DNA in vitro. *Carcinogenesis* 22, 1019-25 (2001).
92. Blount, B. C. & Ames, B. N. DNA damage in folate deficiency. *Baillieres Clin Haematol* 8, 461-78 (1995).
93. Crott, J. W., Mashiyama, S. T., Ames, B. N. & Fenech, M. The effect of folic acid deficiency and MTHFR C677T polymorphism on chromosome damage in human lymphocytes in vitro. *Cancer Epidemiol Biomarkers Prev* 10, 1089-96 (2001).
94. Wang, X., Thomas, P., Xue, J. & Fenech, M. Folate deficiency induces aneuploidy in human lymphocytes in vitro-evidence using cytokinesis-blocked cells and probes specific for chromosomes 17 and 21. *Mutat Res* 551, 167-80 (2004).
95. Beetstra, S., Thomas, P., Salisbury, C., Turner, J. & Fenech, M. Folic acid deficiency increases chromosomal instability, chromosome 21 aneuploidy and sensitivity to radiation-induced micronuclei. *Mutat Res* 578, 317-26 (2005).
96. Evans, A. R., Limp-Foster, M. & Kelley, M. R. Going APE over ref-1. *Mutat Res* 461, 83-108 (2000).
97. Yonekura, S., Nakamura, N., Yonei, S. & Zhang-Akiyama, Q. M. Generation, biological consequences and repair mechanisms of cytosine deamination in DNA. *J Radiat Res (Tokyo)* 50, 19-26 (2009).
98. Duthie, S. J. & Hawdon, A. DNA instability (strand breakage, uracil misincorporation, and defective repair) is increased by folic acid depletion in human lymphocytes in vitro. *Faseb J* 12, 1491-7 (1998).
99. Mashiyama, S. T. *et al.* Uracil in DNA, determined by an improved assay, is increased when deoxynucleosides are added to folate-deficient cultured human lymphocytes. *Anal Biochem* 330, 58-69 (2004).
100. Toussaint, M., Dionne, I. & Wellinger, R. J. Limited TTP supply affects telomere length regulation in a telomerase-independent fashion. *Nucleic Acids Res* 33, 704-13 (2005).

101. Oikawa, S. & Kawanishi, S. Site-specific DNA damage at GGG sequence by oxidative stress may accelerate telomere shortening. *FEBS Lett* 453, 365-8 (1999).
102. von Zglinicki, T. Oxidative stress shortens telomeres. *Trends Biochem Sci* 27, 339-44 (2002).
103. de Lange, T. Shelterin: the protein complex that shapes and safeguards human telomeres. *Genes Dev* 19, 2100-10 (2005).
104. Blackburn, E. H. Structure and function of telomeres. *Nature* 350, 569-73 (1991).
105. Klapper, W., Parwaresch, R. & Krupp, G. Telomere biology in human aging and aging syndromes. *Mech Ageing Dev* 122, 695-712 (2001).
106. Jang, J. *et al.* Telomere length and the risk of lung cancer. *Cancer Sci.* Apr 29 (2008).
107. Griffith, J. K. *et al.* Reduced telomere DNA content is correlated with genomic instability and metastasis in invasive human breast carcinoma. *Breast Cancer Res Treat* 54, 59-64 (1999).
108. Plentz, R. R. *et al.* Telomere shortening of epithelial cells characterises the adenoma-carcinoma transition of human colorectal cancer. *Gut* 52, 1304-7 (2003).
109. Meeker, A. K. Telomeres and telomerase in prostatic intraepithelial neoplasia and prostate cancer biology. *Urol Oncol* 24, 122-30 (2006).
110. Sieglova, Z. *et al.* Dynamics of telomere erosion and its association with genome instability in myelodysplastic syndromes (MDS) and acute myelogenous leukemia arising from MDS: a marker of disease prognosis? *Leuk Res* 28, 1013-21 (2004).
111. Puzianowska-Kuznicka, M. & Kuznicki, J. Genetic alterations in accelerated ageing syndromes. Do they play a role in natural ageing? *Int J Biochem Cell Biol* 37, 947-60 (2005).
112. Krtolica, A. Stem cell: balancing aging and cancer. *Int J Biochem Cell Biol* 37, 935-41 (2005).
113. Rodier, F., Kim, S. H., Nijjar, T., Yaswen, P. & Campisi, J. Cancer and aging: the importance of telomeres in genome maintenance. *Int J Biochem Cell Biol* 37, 977-90 (2005).
114. Liu, Q. *et al.* Effects of trace elements on the telomere lengths of hepatocytes L-02 and hepatoma cells SMMC-7721. *Biol Trace Elem Res* 100, 215-27 (2004).
115. von Zglinicki, T., Burkle, A. & Kirkwood, T. B. Stress, DNA damage and ageing -- an integrative approach. *Exp Gerontol* 36, 1049-62 (2001).
116. Neri, M. *et al.* Micronuclei frequency in children exposed to environmental mutagens: a review. *Mutat Res* 544, 243-54 (2003).

117. Bonassi, S. *et al.* Effect of smoking habit on the frequency of micronuclei in human lymphocytes: results from the Human MicroNucleus project. *Mutat Res* 543, 155-66 (2003).
118. Crott, J. W. & Fenech, M. Effect of vitamin C supplementation on chromosome damage, apoptosis and necrosis ex vivo. *Carcinogenesis* 20, 1035-41 (1999).
119. Hayflick, L. & Moorhead, P. S. The serial cultivation of human diploid cell strains. *Exp Cell Res* 25, 585-621 (1961).
120. Ben-Porath, I. & Weinberg, R. A. When cells get stressed: an integrative view of cellular senescence. *J Clin Invest* 113, 8-13 (2004).
121. Olovnikov, A. M. [Principle of marginotomy in template synthesis of polynucleotides]. *Dokl Akad Nauk SSSR* 201, 1496-9 (1971).
122. Harley, C. B., Futcher, A. B. & Greider, C. W. Telomeres shorten during ageing of human fibroblasts. *Nature* 345, 458-60 (1990).
123. Baird, D. M., Rowson, J., Wynford-Thomas, D. & Kipling, D. Extensive allelic variation and ultrashort telomeres in senescent human cells. *Nat Genet* 33, 203-7 (2003).
124. Tominaga, K., Olgun, A., Smith, J. R. & Pereira-Smith, O. M. Genetics of cellular senescence. *Mech Ageing Dev* 123, 927-36 (2002).
125. Capper, R. *et al.* The nature of telomere fusion and a definition of the critical telomere length in human cells. *Genes Dev* 21, 2495-508 (2007).
126. Hayflick, L. The future of ageing. *Nature* 408, 267-9 (2000).
127. Iwama, H. *et al.* Telomeric length and telomerase activity vary with age in peripheral blood cells obtained from normal individuals. *Hum Genet* 102, 397-402 (1998).
128. Rufer, N. *et al.* Telomere fluorescence measurements in granulocytes and T lymphocyte subsets point to a high turnover of hematopoietic stem cells and memory T cells in early childhood. *J Exp Med* 190, 157-67 (1999).
129. Mayer, S. *et al.* Sex-specific telomere length profiles and age-dependent erosion dynamics of individual chromosome arms in humans. *Cytogenet Genome Res* 112, 194-201 (2006).
130. Bekaert, S. *et al.* Telomere length and cardiovascular risk factors in a middle-aged population free of overt cardiovascular disease. *Aging Cell* 6, 639-47 (2007).
131. Martens, U. M. *et al.* Short telomeres on human chromosome 17p. *Nat Genet* 18, 76-80 (1998).
132. Aviv, A., Shay, J., Christensen, K. & Wright, W. The longevity gender gap: are telomeres the explanation? *Sci Aging Knowledge Environ* 2005, pe16 (2005).

133. Bayne, S. *et al.* Estrogen deficiency leads to telomerase inhibition, telomere shortening and reduced cell proliferation in the adrenal gland of mice. *Cell Res* 18, 1141-50 (2008).
134. Epel, E. S. *et al.* Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci U S A* 101, 17312-5 (2004).
135. Morla, M. *et al.* Telomere shortening in smokers with and without COPD. *Eur Respir J* 27, 525-8 (2006).
136. McGrath, M., Wong, J. Y., Michaud, D., Hunter, D. J. & De Vivo, I. Telomere length, cigarette smoking, and bladder cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev* 16, 815-9 (2007).
137. Valdes, A. M. *et al.* Obesity, cigarette smoking, and telomere length in women. *Lancet* 366, 662-4 (2005).
138. Zannolli, R. *et al.* Telomere length and obesity. *Acta Paediatr* 97, 952-4 (2008).
139. Opresko, P., Fan, J., Danzy, S., Wilson, D. M. & Bohr, V. Oxidative damage in telomeric DNA disrupts recognition by TRF1 and TRF2. *Nucleic Acids Res* Feb 24; 33, 1230-1239 (2005).
140. Epel, E. S. Psychological and metabolic stress: a recipe for accelerated cellular aging? *Hormones (Athens)* 8, 7-22 (2009).
141. Graakjaer, J. *et al.* The relative lengths of individual telomeres are defined in the zygote and strictly maintained during life. *Aging Cell* 3, 97-102 (2004).
142. Slagboom, P. E., Droog, S. & Boomsma, D. I. Genetic determination of telomere size in humans: a twin study of three age groups. *Am J Hum Genet* 55, 876-82 (1994).
143. Njajou, O. T. *et al.* Telomere length is paternally inherited and is associated with parental lifespan. *Proc Natl Acad Sci U S A* 104, 12135-9 (2007).
144. Nordfjall, K., Larefalk, A., Lindgren, P., Holmberg, D. & Roos, G. Telomere length and heredity: Indications of paternal inheritance. *Proc Natl Acad Sci U S A* 102, 16374-8 (2005).
145. Unry, B. M., Cook, L. S. & Riabowol, K. T. Paternal age is positively linked to telomere length of children. *Aging Cell* 4, 97-101 (2005).
146. Graakjaer, J. *et al.* Allele-specific relative telomere lengths are inherited. *Hum Genet* 119, 344-50 (2006).
147. Riethman, H., Ambrosini, A. & Paul, S. Human subtelomere structure and variation. *Chromosome Res* 13, 505-15 (2005).
148. Blasco, M. A. The epigenetic regulation of mammalian telomeres. *Nat Rev Genet* 8, 299-309 (2007).
149. Blackburn, E. H. Switching and signaling at the telomere. *Cell* 106, 661-73 (2001).

150. Smith, S. & de Lange, T. Cell cycle dependent localization of the telomeric PARP, tankyrase, to nuclear pore complexes and centrosomes. *J Cell Sci* 112 (Pt 21), 3649-56 (1999).
151. Houghtaling, B. R., Cuttonaro, L., Chang, W. & Smith, S. A dynamic molecular link between the telomere length regulator TRF1 and the chromosome end protector TRF2. *Curr Biol* 14, 1621-31 (2004).
152. Chebel, A. *et al.* Telomere uncapping during in vitro T-lymphocyte senescence. *Aging Cell* 8, 52-64 (2009).
153. Martinez, P. *et al.* Increased telomere fragility and fusions resulting from TRF1 deficiency lead to degenerative pathologies and increased cancer in mice. *Genes Dev* 23, 2060-75 (2009).
154. Lee, M. E. *et al.* Variation of the 3' telomeric overhang lengths in human cells. *Cancer Lett* 264, 107-18 (2008).
155. Greider, C. W. Telomeres do D-loop-T-loop. *Cell* 97, 419-22 (1999).
156. Griffith, J. D. *et al.* Mammalian telomeres end in a large duplex loop. *Cell* 97, 503-14 (1999).
157. Xin, H. *et al.* TPP1 is a homologue of ciliate TEBP-beta and interacts with POT1 to recruit telomerase. *Nature* 445, 559-62 (2007).
158. Baumgartner, B. L. & Lundblad, V. Telomere identity crisis. *Genes Dev* 19, 2522-5 (2005).
159. Kondo, T. *et al.* Expression of POT1 is associated with tumor stage and telomere length in gastric carcinoma. *Cancer Res* 64, 523-9 (2004).
160. Wellinger, R. J., Wolf, A. J. & Zakian, V. A. Saccharomyces telomeres acquire single-strand TG1-3 tails late in S phase. *Cell* 72, 51-60 (1993).
161. Wellinger, R. J., Wolf, A. J. & Zakian, V. A. Origin activation and formation of single-strand TG1-3 tails occur sequentially in late S phase on a yeast linear plasmid. *Mol Cell Biol* 13, 4057-65 (1993).
162. Wellinger, R. J., Wolf, A. J. & Zakian, V. A. Structural and temporal analysis of telomere replication in yeast. *Cold Spring Harb Symp Quant Biol* 58, 725-32 (1993).
163. Fairall, L., Chapman, L., Moss, H., de Lange, T. & Rhodes, D. Structure of the TRFH dimerization domain of the human telomeric proteins TRF1 and TRF2. *Mol Cell* 8, 351-61 (2001).
164. Kim, H. *et al.* TRF2 functions as a protein hub and regulates telomere maintenance by recognizing specific peptide motifs. *Nat Struct Mol Biol* 16, 372-9 (2009).
165. Okamoto, K. & Shinkai, Y. TRFH domain is critical for TRF1-mediated telomere stabilization. *Cell Struct Funct* 34, 71-6 (2009).

166. Broccoli, D., Smogorzewska, A., Chong, L. & de Lange, T. Human telomeres contain two distinct Myb-related proteins, TRF1 and TRF2. *Nat Genet* 17, 231-5 (1997).
167. Blasco, M. A. Telomeres and human disease: ageing, cancer and beyond. *Nat Rev Genet* 6, 611-22 (2005).
168. van Steensel, B. & de Lange, T. Control of telomere length by the human telomeric protein TRF1. *Nature* 385, 740-3 (1997).
169. Munoz, P. *et al.* TRF1 controls telomere length and mitotic fidelity in epithelial homeostasis. *Mol Cell Biol* 29, 1608-25 (2009).
170. Okamoto, K., Iwano, T., Tachibana, M. & Shinkai, Y. Distinct roles of TRF1 in the regulation of telomere structure and lengthening. *J Biol Chem* 283, 23981-8 (2008).
171. de Lange, T. Protection of mammalian telomeres. *Oncogene* 21, 532-40 (2002).
172. van Steensel, B., Smogorzewska, A. & de Lange, T. TRF2 protects human telomeres from end-to-end fusions. *Cell* 92, 401-13 (1998).
173. Bailey, S. M., Cornforth, M. N., Kurimasa, A., Chen, D. J. & Goodwin, E. H. Strand-specific postreplicative processing of mammalian telomeres. *Science* 293, 2462-5 (2001).
174. Karlseder, J. *et al.* The telomeric protein TRF2 binds the ATM kinase and can inhibit the ATM-dependent DNA damage response. *PLoS Biol* 2, E240 (2004).
175. Bradshaw, P. S., Stavropoulos, D. J. & Meyn, M. S. Human telomeric protein TRF2 associates with genomic double-strand breaks as an early response to DNA damage. *Nat Genet* 37, 193-7 (2005).
176. Karlseder, J., Broccoli, D., Dai, Y., Hardy, S. & de Lange, T. p53- and ATM-dependent apoptosis induced by telomeres lacking TRF2. *Science* 283, 1321-5 (1999).
177. Richter, T. *et al.* TRF2 overexpression diminishes repair of telomeric single-strand breaks and accelerates telomere shortening in human fibroblasts. *Mech Ageing Dev* 128, 340-5 (2007).
178. Blackburn, E. H. *et al.* Recognition and elongation of telomeres by telomerase. *Genome* 31, 553-60 (1989).
179. Bodnar, A. G. *et al.* Extension of life-span by introduction of telomerase into normal human cells. *Science* 279, 349-52 (1998).
180. Holt, S. E., Wright, W. E. & Shay, J. W. Multiple pathways for the regulation of telomerase activity. *Eur J Cancer* 33, 761-6 (1997).
181. Greider, C. W. Telomerase activity, cell proliferation, and cancer. *Proc Natl Acad Sci U S A* 95, 90-2 (1998).
182. Cohen, S. B. *et al.* Protein composition of catalytically active human telomerase from immortal cells. *Science* 315, 1850-3 (2007).

183. Stern, J. L. & Bryan, T. M. Telomerase recruitment to telomeres. *Cytogenet Genome Res* 122, 243-54 (2008).
184. Ng, L. J., Cropley, J. E., Pickett, H. A., Reddel, R. R. & Suter, C. M. Telomerase activity is associated with an increase in DNA methylation at the proximal subtelomere and a reduction in telomeric transcription. *Nucleic Acids Res* 37, 1152-9 (2009).
185. Azzalin, C. M., Reichenbach, P., Khoriauli, L., Giulotto, E. & Lingner, J. Telomeric repeat containing RNA and RNA surveillance factors at mammalian chromosome ends. *Science* 318, 798-801 (2007).
186. Schoeftner, S. & Blasco, M. A. Developmentally regulated transcription of mammalian telomeres by DNA-dependent RNA polymerase II. *Nat Cell Biol* 10, 228-36 (2008).
187. Tsakiri, K. D. *et al.* Adult-onset pulmonary fibrosis caused by mutations in telomerase. *Proc Natl Acad Sci U S A* 104, 7552-7 (2007).
188. Armanios, M. Y. *et al.* Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl J Med* 356, 1317-26 (2007).
189. Vulliamy, T., Marrone, A., Dokal, I. & Mason, P. J. Association between aplastic anaemia and mutations in telomerase RNA. *Lancet* 359, 2168-70 (2002).
190. Xin, Z. T. *et al.* Functional characterization of natural telomerase mutations found in patients with hematologic disorders. *Blood* 109, 524-32 (2007).
191. Liang, J. *et al.* Mutations in telomerase catalytic protein in Japanese children with aplastic anemia. *Haematologica* 91, 656-8 (2006).
192. Yamaguchi, H. *et al.* Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. *N Engl J Med* 352, 1413-24 (2005).
193. Ly, H. *et al.* Functional characterization of telomerase RNA variants found in patients with hematologic disorders. *Blood* 105, 2332-9 (2005).
194. Ohyashiki, K., Shay, J. W. & Ohyashiki, J. H. Lack of mutations of the human telomerase RNA gene (hTERC) in myelodysplastic syndrome. *Haematologica* 90, 691 (2005).
195. Ohyashiki, J. H. *et al.* Quantitative relationship between functionally active telomerase and major telomerase components (hTERT and hTR) in acute leukaemia cells. *Br J Cancer* 92, 1942-7 (2005).
196. Matsubara, Y. *et al.* Coronary artery disease and a functional polymorphism of hTERT. *Biochem Biophys Res Commun* 348, 669-72 (2006).
197. Reddel, R. R. Alternative lengthening of telomeres, telomerase, and cancer. *Cancer Lett* 194, 155-62 (2003).
198. Mabruk, M. J. & O'Flatharta, C. Telomerase: is it the future diagnostic and prognostic tool in human cancer? *Expert Rev Mol Diagn* 5, 907-16 (2005).

199. Cesare, A. J. & Reddel, R. R. Telomere uncapping and alternative lengthening of telomeres. *Mech Ageing Dev* 129, 99-108 (2008).
200. Meeker, A. K. & De Marzo, A. M. Recent advances in telomere biology: implications for human cancer. *Curr Opin Oncol* 16, 32-8 (2004).
201. Raynaud, C. M. *et al.* Telomere shortening is correlated with the DNA damage response and telomeric protein down-regulation in colorectal preneoplastic lesions. *Ann Oncol* 19, 1875-81 (2008).
202. Blackburn, E. H. Telomeres and telomerase: their mechanisms of action and the effects of altering their functions. *FEBS Lett* 579, 859-62 (2005).
203. Simon, N. M. *et al.* Telomere shortening and mood disorders: preliminary support for a chronic stress model of accelerated aging. *Biol Psychiatry* 60, 432-5 (2006).
204. Martin-Ruiz, C. *et al.* Telomere length predicts poststroke mortality, dementia, and cognitive decline. *Ann Neurol* 60, 174-80 (2006).
205. Panossian, L. A. *et al.* Telomere shortening in T cells correlates with Alzheimer's disease status. *Neurobiol Aging* 24, 77-84 (2003).
206. Okuda, K. *et al.* Telomere attrition of the human abdominal aorta: relationships with age and atherosclerosis. *Atherosclerosis* 152, 391-8 (2000).
207. Epel, E. S. *et al.* Cell aging in relation to stress arousal and cardiovascular disease risk factors. *Psychoneuroendocrinology* 31, 277-87 (2006).
208. Jeanclos, E. *et al.* Shortened telomere length in white blood cells of patients with IDDM. *Diabetes* 47, 482-6 (1998).
209. Adaikalakoteswari, A., Balasubramanyam, M. & Mohan, V. Telomere shortening occurs in Asian Indian Type 2 diabetic patients. *Diabet Med* 22, 1151-6 (2005).
210. Steer, S. E. *et al.* Reduced telomere length in rheumatoid arthritis is independent of disease activity and duration. *Ann Rheum Dis* 66, 476-80 (2007).
211. Kitada, T., Seki, S., Kawakita, N., Kuroki, T. & Monna, T. Telomere shortening in chronic liver diseases. *Biochem Biophys Res Commun* 211, 33-9 (1995).
212. Meeker, A. K. *et al.* Telomere length abnormalities occur early in the initiation of epithelial carcinogenesis. *Clin Cancer Res* 10, 3317-26 (2004).
213. Bisoffi, M., Heaphy, C. M. & Griffith, J. K. Telomeres: prognostic markers for solid tumors. *Int J Cancer* 119, 2255-60 (2006).
214. Askree, S. H. *et al.* A genome-wide screen for *Saccharomyces cerevisiae* deletion mutants that affect telomere length. *Proc Natl Acad Sci U S A* 101, 8658-63 (2004).
215. Gatbonton, T. *et al.* Telomere length as a quantitative trait: genome-wide survey and genetic mapping of telomere length-control genes in yeast. *PLoS Genet* 2, e35 (2006).

216. Rigolin, G. M. *et al.* Flow cytometric detection of accelerated telomere shortening in myelodysplastic syndromes: correlations with aetiological and clinical-biological findings. *Eur J Haematol* 73, 351-8 (2004).
217. Hartmann, U. *et al.* Telomere length and hTERT expression in patients with acute myeloid leukemia correlates with chromosomal abnormalities. *Haematologica* 90, 307-16 (2005).
218. Brummendorf, T. H. *et al.* Prognostic implications of differences in telomere length between normal and malignant cells from patients with chronic myeloid leukemia measured by flow cytometry. *Blood* 95, 1883-90 (2000).
219. Bechter, O. E. *et al.* Telomere length and telomerase activity predict survival in patients with B cell chronic lymphocytic leukemia. *Cancer Res* 58, 4918-22 (1998).
220. Oh, B. K. *et al.* High telomerase activity and long telomeres in advanced hepatocellular carcinomas with poor prognosis. *Lab Invest* 88, 144-52 (2008).
221. Patel, M. M. *et al.* Clinical usefulness of telomerase activation and telomere length in head and neck cancer. *Head Neck* 24, 1060-7 (2002).
222. Ohali, A. *et al.* Telomere length is a prognostic factor in neuroblastoma. *Cancer* 107, 1391-9 (2006).
223. Garcia-Aranda, C. *et al.* Correlations of telomere length, telomerase activity, and telomeric-repeat binding factor 1 expression in colorectal carcinoma. *Cancer* 106, 541-51 (2006).
224. Gertler, R. *et al.* Telomere length and human telomerase reverse transcriptase expression as markers for progression and prognosis of colorectal carcinoma. *J Clin Oncol* 22, 1807-14 (2004).
225. Gertler, R., Doll, D., Maak, M., Feith, M. & Rosenberg, R. Telomere length and telomerase subunits as diagnostic and prognostic biomarkers in Barrett carcinoma. *Cancer* 112, 2173-80 (2008).
226. Rudolph, K. L., Millard, M., Bosenberg, M. W. & DePinho, R. A. Telomere dysfunction and evolution of intestinal carcinoma in mice and humans. *Nat Genet* 28, 155-9 (2001).
227. Odagiri, E. *et al.* Reduction of telomeric length and c-erbB-2 gene amplification in human breast cancer, fibroadenoma, and gynecomastia. Relationship to histologic grade and clinical parameters. *Cancer* 73, 2978-84 (1994).
228. Fordyce, C. A. *et al.* Telomere content correlates with stage and prognosis in breast cancer. *Breast Cancer Res Treat* 99, 193-202 (2006).

229. Heaphy, C. M., Baumgartner, K. B., Bisoffi, M., Baumgartner, R. N. & Griffith, J. K. Telomere DNA content predicts breast cancer-free survival interval. *Clin Cancer Res* 13, 7037-43 (2007).
230. Donaldson, L. *et al.* Association between outcome and telomere DNA content in prostate cancer. *J Urol* 162, 1788-92 (1999).
231. Fordyce, C. A. *et al.* Association between cancer-free survival and telomere DNA content in prostate tumors. *J Urol* 173, 610-4 (2005).
232. Frias, C. *et al.* Telomere shortening is associated with poor prognosis and telomerase activity correlates with DNA repair impairment in non-small cell lung cancer. *Lung Cancer* 60, 416-25 (2008).
233. Hirashima, T. *et al.* Prognostic significance of telomeric repeat length alterations in pathological stage I-IIIA non-small cell lung cancer. *Anticancer Res* 20, 2181-7 (2000).
234. Shirotani, Y. *et al.* Alteration in length of telomeric repeats in lung cancer. *Lung Cancer* 11, 29-41 (1994).
235. Svenson, U., Ljungberg, B. & Roos, G. Telomere length in peripheral blood predicts survival in clear cell renal cell carcinoma. *Cancer Res* 69, 2896-901 (2009).
236. Hiyama, E. *et al.* Telomerase activity in neuroblastoma: is it a prognostic indicator of clinical behaviour? *Eur J Cancer* 33, 1932-6 (1997).
237. Wu, X. *et al.* Telomere dysfunction: a potential cancer predisposition factor. *J Natl Cancer Inst* 95, 1211-8 (2003).
238. Nordfjall, K. *et al.* The individual blood cell telomere attrition rate is telomere length dependent. *PLoS Genet* 5, e1000375 (2009).
239. Svenson, U. *et al.* Breast cancer survival is associated with telomere length in peripheral blood cells. *Cancer Res* 68, 3618-23 (2008).
240. Crabbe, L., Jauch, A., Naeger, C. M., Holtgreve-Grez, H. & Karlseder, J. Telomere dysfunction as a cause of genomic instability in Werner syndrome. *Proc Natl Acad Sci U S A* 104, 2205-10 (2007).
241. Schonberg, S., Niermeijer, M. F., Bootsma, D., Henderson, E. & German, J. Werner's syndrome: proliferation in vitro of clones of cells bearing chromosome translocations. *Am J Hum Genet* 36, 387-97 (1984).
242. Lavin, M. F. & Kozlov, S. ATM activation and DNA damage response. *Cell Cycle* 6, 931-42 (2007).
243. Drummond, M. W., Balabanov, S., Holyoake, T. L. & Brummendorf, T. H. Concise review: Telomere biology in normal and leukemic hematopoietic stem cells. *Stem Cells* 25, 1853-61 (2007).

244. Callen, E. *et al.* Breaks at telomeres and TRF2-independent end fusions in Fanconi anemia. *Hum Mol Genet* 11, 439-44 (2002).
245. Shiloh, Y. ATM and related protein kinases: safeguarding genome integrity. *Nat Rev Cancer* 3, 155-68 (2003).
246. d'Adda di Fagagna, F., Teo, S. H. & Jackson, S. P. Functional links between telomeres and proteins of the DNA-damage response. *Genes Dev* 18, 1781-99 (2004).
247. Raynaud, C. M., Sabatier, L., Philipot, O., Olaussen, K. A. & Soria, J. C. Telomere length, telomeric proteins and genomic instability during the multistep carcinogenic process. *Crit Rev Oncol Hematol* 66, 99-117 (2008).
248. Slijepcevic, P. & Al-Wahiby, S. Telomere biology: integrating chromosomal end protection with DNA damage response. *Chromosoma* 114, 275-85 (2005).
249. d'Adda di Fagagna, F. *et al.* A DNA damage checkpoint response in telomere-initiated senescence. *Nature* 426, 194-8 (2003).
250. d'Adda di Fagagna, F. Living on a break: cellular senescence as a DNA-damage response. *Nat Rev Cancer* 8, 512-22 (2008).
251. Bassing, C. H. & Alt, F. W. The cellular response to general and programmed DNA double strand breaks. *DNA Repair (Amst)* 3, 781-96 (2004).
252. Smith, G. C., Divecha, N., Lakin, N. D. & Jackson, S. P. DNA-dependent protein kinase and related proteins. *Biochem Soc Symp* 64, 91-104 (1999).
253. Downs, J. A. *et al.* Binding of chromatin-modifying activities to phosphorylated histone H2A at DNA damage sites. *Mol Cell* 16, 979-90 (2004).
254. Mitchell, J. R., Hoeijmakers, J. H. & Niedernhofer, L. J. Divide and conquer: nucleotide excision repair battles cancer and ageing. *Curr Opin Cell Biol* 15, 232-40 (2003).
255. Hoeijmakers, J. H. Genome maintenance mechanisms for preventing cancer. *Nature* 411, 366-74 (2001).
256. Wilson, D. M., 3rd & Bohr, V. A. The mechanics of base excision repair, and its relationship to aging and disease. *DNA Repair (Amst)* 6, 544-59 (2007).
257. Takai, H., Smogorzewska, A. & de Lange, T. DNA damage foci at dysfunctional telomeres. *Curr Biol* 13, 1549-56 (2003).
258. Hande, M. P., Balajee, A. S., Tchirkov, A., Wynshaw-Boris, A. & Lansdorp, P. M. Extra-chromosomal telomeric DNA in cells from Atm(-/-) mice and patients with ataxia-telangiectasia. *Hum Mol Genet* 10, 519-28 (2001).
259. Lustig, A. J. & Petes, T. D. Identification of yeast mutants with altered telomere structure. *Proc Natl Acad Sci U S A* 83, 1398-402 (1986).

260. Greenwell, P. W. *et al.* TEL1, a gene involved in controlling telomere length in *S. cerevisiae*, is homologous to the human ataxia telangiectasia gene. *Cell* 82, 823-9 (1995).
261. Boulton, S. J. & Jackson, S. P. Identification of a *Saccharomyces cerevisiae* Ku80 homologue: roles in DNA double strand break rejoining and in telomeric maintenance. *Nucleic Acids Res* 24, 4639-48 (1996).
262. Porter, S. E., Greenwell, P. W., Ritchie, K. B. & Petes, T. D. The DNA-binding protein Hdf1p (a putative Ku homologue) is required for maintaining normal telomere length in *Saccharomyces cerevisiae*. *Nucleic Acids Res* 24, 582-5 (1996).
263. Baumann, P. & Cech, T. R. Protection of telomeres by the Ku protein in fission yeast. *Mol Biol Cell* 11, 3265-75 (2000).
264. Hsu, H. L., Gilley, D., Blackburn, E. H. & Chen, D. J. Ku is associated with the telomere in mammals. *Proc Natl Acad Sci U S A* 96, 12454-8 (1999).
265. d'Adda di Fagagna, F. *et al.* Effects of DNA nonhomologous end-joining factors on telomere length and chromosomal stability in mammalian cells. *Curr Biol* 11, 1192-6 (2001).
266. Hsu, H. L. *et al.* Ku acts in a unique way at the mammalian telomere to prevent end joining. *Genes Dev* 14, 2807-12 (2000).
267. Song, K., Jung, D., Jung, Y., Lee, S. G. & Lee, I. Interaction of human Ku70 with TRF2. *FEBS Lett* 481, 81-5 (2000).
268. Peterson, S. E. *et al.* The function of a stem-loop in telomerase RNA is linked to the DNA repair protein Ku. *Nat Genet* 27, 64-7 (2001).
269. Bailey, S. M. *et al.* DNA double-strand break repair proteins are required to cap the ends of mammalian chromosomes. *Proc Natl Acad Sci U S A* 96, 14899-904 (1999).
270. Gilley, D. *et al.* DNA-PKcs is critical for telomere capping. *Proc Natl Acad Sci U S A* 98, 15084-8 (2001).
271. Ricchetti, M., Dujon, B. & Fairhead, C. Distance from the chromosome end determines the efficiency of double strand break repair in subtelomeres of haploid yeast. *J Mol Biol* 328, 847-62 (2003).
272. Michelson, R. J., Rosenstein, S. & Weinert, T. A telomeric repeat sequence adjacent to a DNA double-stranded break produces an anticheckpoint. *Genes Dev* 19, 2546-59 (2005).
273. Petersen, S., Saretzki, G. & von Zglinicki, T. Preferential accumulation of single-stranded regions in telomeres of human fibroblasts. *Exp Cell Res* 239, 152-60 (1998).
274. Kruk, P. A., Rampino, N. J. & Bohr, V. A. DNA damage and repair in telomeres: relation to aging. *Proc Natl Acad Sci U S A* 92, 258-62 (1995).

275. Mitelman, F., Johansson, B. & Mertens, F. The impact of translocations and gene fusions on cancer causation. *Nat Rev Cancer* 7, 233-45 (2007).
276. Gisselsson, D. & Hoglund, M. Connecting mitotic instability and chromosome aberrations in cancer--can telomeres bridge the gap? *Semin Cancer Biol* 15, 13-23 (2005).
277. Gisselsson, D. Mitotic instability in cancer: is there method in the madness? *Cell Cycle* 4, 1007-10 (2005).
278. Stewenius, Y. *et al.* Structural and numerical chromosome changes in colon cancer develop through telomere-mediated anaphase bridges, not through mitotic multipolarity. *Proc Natl Acad Sci U S A* 102, 5541-6 (2005).
279. Gisselsson, D. *et al.* Telomere dysfunction triggers extensive DNA fragmentation and evolution of complex chromosome abnormalities in human malignant tumors. *Proc Natl Acad Sci U S A* 98, 12683-8 (2001).
280. McClintock, B. The Fusion of Broken Ends of Chromosomes Following Nuclear Fusion. *Proc Natl Acad Sci U S A* 28, 458-63 (1942).
281. Cheung, A. & Deng, W. Telomere dysfunction, genome instability and cancer. *Front Biosci.* Jan 1, 2075-90 (2008).
282. Shimizu, N., Shingaki, K., Kaneko-Sasaguri, Y., Hashizume, T. & Kanda, T. When, where and how the bridge breaks: anaphase bridge breakage plays a crucial role in gene amplification and HSR generation. *Exp Cell Res* 302, 233-43 (2005).
283. Chin, K. *et al.* In situ analyses of genome instability in breast cancer. *Nat Genet* 36, 984-8 (2004).
284. DePinho, R. A. & Polyak, K. Cancer chromosomes in crisis. *Nat Genet* 36, 932-4 (2004).
285. Ames, B. N. Micronutrient deficiencies. A major cause of DNA damage. *Ann N Y Acad Sci* 889, 87-106 (1999).
286. Wilson, P. M. *et al.* Novel opportunities for thymidylate metabolism as a therapeutic target. *Mol Cancer Ther* 7, 3029-37 (2008).
287. Bouffler, S. D. Involvement of telomeric sequences in chromosomal aberrations. *Mutat Res* 404, 199-204 (1998).
288. Rufer, N., Dragowska, W., Thornbury, G., Roosnek, E. & Lansdorp, P. M. Telomere length dynamics in human lymphocyte subpopulations measured by flow cytometry. *Nat Biotechnol* 16, 743-7 (1998).
289. Baerlocher, G. M., Mak, J., Tien, T. & Lansdorp, P. M. Telomere length measurement by fluorescence in situ hybridization and flow cytometry: tips and pitfalls. *Cytometry* 47, 89-99 (2002).

290. Beetstra, S. & Fenech, M. Folic acid deficiency is genotoxic and increases sensitivity to chromosome damage by gamma-radiation. *Asia Pac J Clin Nutr* 13, S87 (2004).
291. Natarajan, A. T., Obe, G. in *Mutagenicity: New Horizons in Genetic Toxicology* (ed. Heddle, J. A.) (Academic Press, Inc, New York, 1982).
292. Levy, J. A., Virolainen, M. & Defendi, V. Human lymphoblastoid lines from lymph node and spleen. *Cancer* 22, 517-24 (1968).
293. Carrier, F. *et al.* Characterization of human Gadd45, a p53-regulated protein. *J Biol Chem* 269, 32672-7 (1994).
294. Zhen, W. *et al.* The relative radiosensitivity of TK6 and WI-L2-NS lymphoblastoid cells derived from a common source is primarily determined by their p53 mutational status. *Mutat Res* 346, 85-92 (1995).
295. Carrier, F., Bae, I., Smith, M. L., Ayers, D. M. & Fornace, A. J., Jr. Characterization of the GADD45 response to ionizing radiation in WI-L2-NS cells, a p53 mutant cell line. *Mutat Res* 352, 79-86 (1996).
296. Larsson, I., Lundgren, E., Nilsson, K. & Strannegard, O. A human neoplastic hematopoietic cell line producing a fibroblast type of interferon. *Dev Biol Stand* 42, 193-7 (1979).
297. Jeyapalan, J. *et al.* The role of telomeres in Etoposide induced tumor cell death. *Cell Cycle* 3, 1169-76 (2004).
298. Eastmond, D. A. & Tucker, J. D. Identification of aneuploidy-inducing agents using cytokinesis-blocked human lymphocytes and an antikinetochore antibody. *Environ Mol Mutagen* 13, 34-43 (1989).
299. Hultdin, M. *et al.* Telomere analysis by fluorescence in situ hybridization and flow cytometry. *Nucleic Acids Res* 26, 3651-6 (1998).
300. Nielsen, P. E., Egholm, M., Berg, R. H. & Buchardt, O. Sequence-selective recognition of DNA by strand displacement with a thymine-substituted polyamide. *Science* 254, 1497-500 (1991).
301. Nielsen, P. E. PNA Technology. *Mol Biotechnol* 26, 233-48 (2004).
302. Demidov, V. V., Yavnilovich, M. V., Belotserkovskii, B. P., Frank-Kamenetskii, M. D. & Nielsen, P. E. Kinetics and mechanism of polyamide ("peptide") nucleic acid binding to duplex DNA. *Proc Natl Acad Sci U S A* 92, 2637-41 (1995).
303. Lao, A. I., Su, X. & Aung, K. M. SPR study of DNA hybridization with DNA and PNA probes under stringent conditions. *Biosens Bioelectron* 24, 1717-22 (2009).
304. Gagos, S. *et al.* Unusually stable abnormal karyotype in a highly aggressive melanoma negative for telomerase activity. *Mol Cytogenet* 1, 20 (2008).

305. Lu, T. *et al.* Gene regulation and DNA damage in the ageing human brain. *Nature* 429, 883-91 (2004).
306. Collins, A., Cadet, J., Epe, B. & Gedik, C. Problems in the measurement of 8-oxoguanine in human DNA. Report of a workshop, DNA oxidation, held in Aberdeen, UK, 19-21 January, 1997. *Carcinogenesis* 18, 1833-6 (1997).
307. Helbock, H. J. *et al.* DNA oxidation matters: the HPLC-electrochemical detection assay of 8-oxo-deoxyguanosine and 8-oxo-guanine. *Proc Natl Acad Sci U S A* 95, 288-93 (1998).
308. O'Callaghan, N., Dhillon, V., Thomas, P. & Fenech, M. A quantitative real-time PCR method for absolute telomere length. *Biotechniques* 44, 807-9 (2008).
309. Cawthon, R. M. Telomere measurement by quantitative PCR. *Nucleic Acids Res* 30, e47 (2002).
310. Robertson, K. D. DNA methylation and human disease. *Nat Rev Genet* 6, 597-610 (2005).
311. Schulz, W. A., Steinhoff, C. & Florl, A. R. Methylation of endogenous human retroelements in health and disease. *Curr Top Microbiol Immunol* 310, 211-50 (2006).
312. Clark, S. J., Statham, A., Stirzaker, C., Molloy, P. L. & Frommer, M. DNA methylation: bisulphite modification and analysis. *Nat Protoc* 1, 2353-64 (2006).
313. Pfaffl, M. W. A new mathematical model for relative quantification in real-time RT-PCR. *Nucleic Acids Res* 29, e45 (2001).
314. Abbott. Architect System Homocysteine, Kit insert, Ref 1L71. *Abbott Laboratories, Diagnostic Division, IL USA*.
315. Abbott. Architect System Folate, Kit insert, Ref 6C12. *Abbott Laboratories, Diagnostic Division, IL USA* (2005).
316. Abbott. Architect System B12, Kit insert, Ref C609. *Abbott Laboratories, Diagnostic Division, IL USA* (2007).
317. Benassi, B. & Fenech, M. Alcohol, genome instability and breast cancer. *Asia Pac J Clin Nutr* 13, S55 (2004).
318. Fenech, M. The Genome Health Clinic and Genome Health Nutrigenomics concepts: diagnosis and nutritional treatment of genome and epigenome damage on an individual basis. *Mutagenesis* 20, 255-69 (2005).
319. Vera, E., Canela, A., Fraga, M. F., Esteller, M. & Blasco, M. A. Epigenetic regulation of telomeres in human cancer. *Oncogene* (2008).
320. Seimiya, H. *et al.* Telomere shortening and growth inhibition of human cancer cells by novel synthetic telomerase inhibitors MST-312, MST-295, and MST-1991. *Mol Cancer Ther* 1, 657-65 (2002).

321. Seimiya, H., Muramatsu, Y., Ohishi, T. & Tsuruo, T. Tankyrase 1 as a target for telomere-directed molecular cancer therapeutics. *Cancer Cell* 7, 25-37 (2005).
322. Dynek, J. N. & Smith, S. Resolution of sister telomere association is required for progression through mitosis. *Science* 304, 97-100 (2004).
323. Linhart, H. G. *et al.* Folate deficiency induces genomic uracil misincorporation and hypomethylation but does not increase DNA point mutations. *Gastroenterology* 136, 227-235 e3 (2009).
324. Aisner, D. L., Wright, W. E. & Shay, J. W. Telomerase regulation: not just flipping the switch. *Curr Opin Genet Dev* 12, 80-5 (2002).
325. Guilleret, I. & Benhattar, J. Demethylation of the human telomerase catalytic subunit (hTERT) gene promoter reduced hTERT expression and telomerase activity and shortened telomeres. *Exp Cell Res* 289, 326-34 (2003).
326. Garcia-Cao, M., O'Sullivan, R., Peters, A. H., Jenuwein, T. & Blasco, M. A. Epigenetic regulation of telomere length in mammalian cells by the Suv39h1 and Suv39h2 histone methyltransferases. *Nat Genet* 36, 94-9 (2004).
327. Benetti, R., Garcia-Cao, M. & Blasco, M. A. Telomere length regulates the epigenetic status of mammalian telomeres and subtelomeres. *Nat Genet* 39, 243-50 (2007).
328. Gonzalo, S. *et al.* DNA methyltransferases control telomere length and telomere recombination in mammalian cells. *Nat Cell Biol* 8, 416-24 (2006).
329. Slijepcevic, P., Hande, M. P., Bouffler, S. D., Lansdorp, P. & Bryant, P. E. Telomere length, chromatin structure and chromosome fusigenic potential. *Chromosoma* 106, 413-21 (1997).
330. Vukovic, B. *et al.* Correlating breakage-fusion-bridge events with the overall chromosomal instability and in vitro karyotype evolution in prostate cancer. *Cytogenet Genome Res* 116, 1-11 (2007).
331. Tusell, L., Soler, D., Agostini, M., Pampalona, J. & Genesca, A. The number of dysfunctional telomeres in a cell: one amplifies; more than one translocate. *Cytogenet Genome Res* 122, 315-25 (2008).
332. Slijepcevic, P. Telomeres and mechanisms of Robertsonian fusion. *Chromosoma* 107, 136-40 (1998).
333. Fenech, M. F., Dreosti, I. E. & Rinaldi, J. R. Folate, vitamin B12, homocysteine status and chromosome damage rate in lymphocytes of older men. *Carcinogenesis* 18, 1329-36 (1997).
334. Feinberg, A. P., Ohlsson, R. & Henikoff, S. The epigenetic progenitor origin of human cancer. *Nat Rev Genet* 7, 21-33 (2006).

335. Mulero-Navarro, S. & Esteller, M. Epigenetic biomarkers for human cancer: The time is now. *Crit Rev Oncol Hematol* Apr 18 (2008).
336. Neumeister, P., Albanese, C., Balent, B., Greally, J. & Pestell, R. G. Senescence and epigenetic dysregulation in cancer. *Int J Biochem Cell Biol* 34, 1475-90 (2002).
337. Jones, P. A. & Takai, D. The role of DNA methylation in mammalian epigenetics. *Science* 293, 1068-70 (2001).
338. Yasuda, K. *et al.* Requirement for DNA CpG content in TLR9-dependent dendritic cell activation induced by DNA-containing immune complexes. *J Immunol* 183, 3109-17 (2009).
339. Kass, S. U., Pruss, D. & Wolffe, A. P. How does DNA methylation repress transcription? *Trends Genet* 13, 444-9 (1997).
340. Kass, S. U., Landsberger, N. & Wolffe, A. P. DNA methylation directs a time-dependent repression of transcription initiation. *Curr Biol* 7, 157-65 (1997).
341. Klose, R. J. & Bird, A. P. Genomic DNA methylation: the mark and its mediators. *Trends Biochem Sci* 31, 89-97 (2006).
342. Lopez-Serra, L. *et al.* A profile of methyl-CpG binding domain protein occupancy of hypermethylated promoter CpG islands of tumor suppressor genes in human cancer. *Cancer Res* 66, 8342-6 (2006).
343. Bestor, T. H. The DNA methyltransferases of mammals. *Hum Mol Genet* 9, 2395-402 (2000).
344. Espada, J. *et al.* Human DNA methyltransferase 1 is required for maintenance of the histone H3 modification pattern. *J Biol Chem* 279, 37175-84 (2004).
345. Dong, A. *et al.* Structure of human DNMT2, an enigmatic DNA methyltransferase homolog that displays denaturant-resistant binding to DNA. *Nucleic Acids Res* 29, 439-48 (2001).
346. Ehrlich, M. The ICF syndrome, a DNA methyltransferase 3B deficiency and immunodeficiency disease. *Clin Immunol* 109, 17-28 (2003).
347. Gisselsson, D. *et al.* Interphase chromosomal abnormalities and mitotic missegregation of hypomethylated sequences in ICF syndrome cells. *Chromosoma* 114, 118-26 (2005).
348. Benetti, R. *et al.* Suv4-20h deficiency results in telomere elongation and derepression of telomere recombination. *J Cell Biol* 178, 925-36 (2007).
349. Peters, A. H. *et al.* Loss of the Suv39h histone methyltransferases impairs mammalian heterochromatin and genome stability. *Cell* 107, 323-37 (2001).
350. Goffin, J. & Eisenhauer, E. DNA methyltransferase inhibitors-state of the art. *Ann Oncol* 13, 1699-716 (2002).

351. Kaminskas, E. *et al.* Approval summary: azacitidine for treatment of myelodysplastic syndrome subtypes. *Clin Cancer Res* 11, 3604-8 (2005).
352. Christman, J. K. 5-Azacytidine and 5-aza-2'-deoxycytidine as inhibitors of DNA methylation: mechanistic studies and their implications for cancer therapy. *Oncogene* 21, 5483-95 (2002).
353. Strelmann, C., Brueckner, B., Musch, T., Stopper, H. & Lyko, F. Functional diversity of DNA methyltransferase inhibitors in human cancer cell lines. *Cancer Res* 66, 2794-800 (2006).
354. Satoh, T., Yamamoto, K., Miura, K. F. & Sofuni, T. Region-specific chromatin decondensation and micronucleus formation induced by 5-azacytidine in human TIG-7 cells. *Cytogenet Genome Res* 104, 289-94 (2004).
355. Stopper, H., Korber, C., Gibis, P., Spencer, D. L. & Caspary, W. J. Micronuclei induced by modulators of methylation: analogs of 5-azacytidine. *Carcinogenesis* 16, 1647-50 (1995).
356. Haaf, T. The effects of 5-azacytidine and 5-azadeoxycytidine on chromosome structure and function: implications for methylation-associated cellular processes. *Pharmacol Ther* 65, 19-46 (1995).
357. Palii, S. S., Van Emburgh, B. O., Sankpal, U. T., Brown, K. D. & Robertson, K. D. DNA methylation inhibitor 5-Aza-2'-deoxycytidine induces reversible genome-wide DNA damage that is distinctly influenced by DNA methyltransferases 1 and 3B. *Mol Cell Biol* 28, 752-71 (2008).
358. Henson, J. D., Neumann, A. A., Yeager, T. R. & Reddel, R. R. Alternative lengthening of telomeres in mammalian cells. *Oncogene* 21, 598-610 (2002).
359. Tilman, G. *et al.* Subtelomeric DNA hypomethylation is not required for telomeric sister chromatid exchanges in ALT cells. *Oncogene* 28, 1682-93 (2009).
360. Fang, J. Y. & Xiao, S. D. Folic acid, polymorphism of methyl-group metabolism genes, and DNA methylation in relation to GI carcinogenesis. *J Gastroenterol* 38, 821-9 (2003).
361. Davis, C. D. & Uthus, E. O. DNA methylation, cancer susceptibility, and nutrient interactions. *Exp Biol Med (Maywood)* 229, 988-95 (2004).
362. Ghoshal, K. *et al.* A folate- and methyl-deficient diet alters the expression of DNA methyltransferases and methyl CpG binding proteins involved in epigenetic gene silencing in livers of F344 rats. *J Nutr* 136, 1522-7 (2006).
363. Jacob, R. A. Folate, DNA methylation, and gene expression: factors of nature and nurture. *Am J Clin Nutr* 72, 903-4 (2000).

364. Melnyk, S. *et al.* Uracil misincorporation, DNA strand breaks, and gene amplification are associated with tumorigenic cell transformation in folate deficient/repleted Chinese hamster ovary cells. *Cancer Lett* 146, 35-44 (1999).
365. Berger, S. H., Pittman, D. L. & Wyatt, M. D. Uracil in DNA: consequences for carcinogenesis and chemotherapy. *Biochem Pharmacol* 76, 697-706 (2008).
366. Schrader, C. E., Guikema, J. E., Wu, X. & Stavnezer, J. The roles of APE1, APE2, DNA polymerase beta and mismatch repair in creating S region DNA breaks during antibody class switch. *Philos Trans R Soc Lond B Biol Sci* 364, 645-52 (2009).
367. Begum, N. A. *et al.* Further evidence for involvement of a noncanonical function of uracil DNA glycosylase in class switch recombination. *Proc Natl Acad Sci U S A* 106, 2752-7 (2009).
368. Chan, K. L., North, P. S. & Hickson, I. D. BLM is required for faithful chromosome segregation and its localization defines a class of ultrafine anaphase bridges. *Embo J* 26, 3397-409 (2007).
369. Canudas, S. *et al.* Protein requirements for sister telomere association in human cells. *Embo J* 26, 4867-78 (2007).
370. Smogorzewska, A., Karlseder, J., Holtgreve-Grez, H., Jauch, A. & de Lange, T. DNA ligase IV-dependent NHEJ of deprotected mammalian telomeres in G1 and G2. *Curr Biol* 12, 1635-44 (2002).
371. Zhu, X. D. *et al.* ERCC1/XPF removes the 3' overhang from uncapped telomeres and represses formation of telomeric DNA-containing double minute chromosomes. *Mol Cell* 12, 1489-98 (2003).
372. Celli, G. B. & de Lange, T. DNA processing is not required for ATM-mediated telomere damage response after TRF2 deletion. *Nat Cell Biol* 7, 712-8 (2005).
373. Morrish, T. A. & Greider, C. W. Short telomeres initiate telomere recombination in primary and tumor cells. *PLoS Genet* 5, e1000357 (2009).
374. Yalon, M., Gal, S., Segev, Y., Selig, S. & Skorecki, K. L. Sister chromatid separation at human telomeric regions. *J Cell Sci* 117, 1961-1970 (2004).
375. Blasco, M. Immunosenescence phenotypes in the telomerase knockout mouse. *Springer Semin Immunopathol.* 24, 75-85 (2002).
376. Fuster, J. J. & Andres, V. Telomere Biology and Cardiovascular Disease. *Circ Res* 99, 1167-1180 (2006).
377. DePinho, R. A. & Wong, K. K. The age of cancer: telomeres, checkpoints, and longevity. *J Clin Invest* 111, S9-14 (2003).

378. Wang, X. *et al.* A comparison of folic acid deficiency-induced genomic instability in lymphocytes of breast cancer patients and normal non-cancer controls from a Chinese population in Yunnan. *Mutagenesis* 21, 41-7 (2006).
379. Courtemanche, C., Elson-Schwab, I., Mashiyama, S. T., Kerry, N. & Ames, B. N. Folate deficiency inhibits the proliferation of primary human CD8+ T lymphocytes in vitro. *J Immunol* 173, 3186-92 (2004).
380. Lin, J. *et al.* Analyses and comparisons of telomerase activity and telomere length in human T and B cells: Insights for epidemiology of telomere maintenance. *J Immunol Methods* (2009).
381. Baerlocher, G. M. & Lansdorp, P. M. Telomere length measurements in leukocyte subsets by automated multicolor flow-FISH. *Cytometry A* 55, 1-6 (2003).
382. Effros, R. B., Dagarag, M. & Valenzuela, H. F. In vitro senescence of immune cells. *Exp Gerontol* 38, 1243-9 (2003).
383. Weng, N. P., Hathcock, K. S. & Hodes, R. J. Regulation of telomere length and telomerase in T and B cells: a mechanism for maintaining replicative potential. *Immunity* 9, 151-7 (1998).
384. Weng, N. P. Telomere and adaptive immunity. *Mech Ageing Dev* 129, 60-6 (2008).
385. Valenzuela, H. F. & Effros, R. B. Divergent telomerase and CD28 expression patterns in human CD4 and CD8 T cells following repeated encounters with the same antigenic stimulus. *Clin Immunol* 105, 117-25 (2002).
386. Coelho, P. A., Queiroz-Machado, J. & Sunkel, C. E. Condensin-dependent localisation of topoisomerase II to an axial chromosomal structure is required for sister chromatid resolution during mitosis. *J Cell Sci* 116, 4763-76 (2003).
387. Elhajouji, A., Cunha, M. & Kirsch-Volders, M. Spindle poisons can induce polyploidy by mitotic slippage and micronucleate mononucleates in the cytokinesis-block assay. *Mutagenesis* 13, 193-8 (1998).
388. Kirsch-Volders, M. & Fenech, M. Inclusion of micronuclei in non-divided mononuclear lymphocytes and necrosis/apoptosis may provide a more comprehensive cytokinesis block micronucleus assay for biomonitoring purposes. *Mutagenesis* 16, 51-8 (2001).
389. Norbury, C. & Nurse, P. Animal cell cycles and their control. *Annu Rev Biochem* 61, 441-70 (1992).
390. Richards, J. B. *et al.* Homocysteine levels and leukocyte telomere length. *Atherosclerosis* 200, 271-27 (2008).
391. Australia. Royal College of Pathologists of Australia Manual (V4.0). (2004).

392. Lee, K. M. *et al.* One-carbon metabolism gene polymorphisms and risk of non-Hodgkin lymphoma in Australia. *Hum Genet* 122, 525-33 (2007).
393. Loscalzo, J. The oxidant stress of hyperhomocyst(e)inemia. *J Clin Invest* 98, 5-7 (1996).
394. Tchirkov, A. & Lansdorp, P. M. Role of oxidative stress in telomere shortening in cultured fibroblasts from normal individuals and patients with ataxia-telangiectasia. *Hum Mol Genet* 12, 227-32 (2003).
395. von Zglinicki, T., Saretzki, G., Docke, W. & Lotze, C. Mild hyperoxia shortens telomeres and inhibits proliferation of fibroblasts: a model for senescence? *Exp Cell Res* 220, 186-93 (1995).
396. Endoh, K., Murakami, M., Araki, R., Maruyama, C. & Umegaki, K. Low folate status increases chromosomal damage by X-ray irradiation. *Int J Radiat Biol* 82, 223-30 (2006).
397. Fenech, M. Nutrition and genome health. *Forum Nutr* 60, 49-65 (2007).
398. Hakin-Smith, V. *et al.* Alternative lengthening of telomeres and survival in patients with glioblastoma multiforme. *Lancet* 361, 836-8 (2003).
399. Han, J. *et al.* A prospective study of telomere length and the risk of skin cancer. *J Invest Dermatol* 129, 415-21 (2009).
400. Royle, N. J. *et al.* The role of recombination in telomere length maintenance. *Biochem Soc Trans* 37, 589-95 (2009).
401. Bollmann, F. M. Targeting ALT: the role of alternative lengthening of telomeres in pathogenesis and prevention of cancer. *Cancer Treat Rev* 33, 704-9 (2007).
402. Lee, M. E., Rha, S. Y., Jeung, H. C., Chung, H. C. & Oh, B. K. Subtelomeric DNA methylation and telomere length in human cancer cells. *Cancer Lett* 281, 82-91 (2009).
403. Mitchell, T. R., Glenfield, K., Jeyanthan, K. & Zhu, X. D. Arginine methylation regulates telomere length and stability. *Mol Cell Biol* 29, 4918-34 (2009).
404. Chen, Y. J. *et al.* Association of mutant TP53 with alternative lengthening of telomeres and favorable prognosis in glioma. *Cancer Res* 66, 6473-6 (2006).
405. Sood, A. K. *et al.* p53 null mutations are associated with a telomerase negative phenotype in ovarian carcinoma. *Cancer Biol Ther* 1, 511-7 (2002).
406. Xu, Q. *et al.* Multivitamin use and telomere length in women. *Am J Clin Nutr* 89, 1857-63 (2009).
407. Paul, L. *et al.* Telomere length in peripheral blood mononuclear cells is associated with folate status in men. *J Nutr* 139, 1273-8 (2009).

APPENDICES: PAPER REPRINTS

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