

# References

- [1] Mendel, G. Versuche über Pflanzen-Hybriden. *Verhandlungen des Naturforschenden Vereines, Abhandlungen*, Brünn **4**, 3–47 (1866).
- [2] Paweletz, N. Walther Flemming: pioneer of mitosis research. *Nat Rev Mol Cell Biol* **2**, 72–5 (2001).
- [3] Allen, G. E. Mendel and modern genetics: the legacy for today. *Endeavour* **27**, 63–8 (2003).
- [4] Sutton, W. S. On the Morphology of the Chromosome group in *Brachystola Magna*. *Biol Bull* **4**, 24–39 (1902).
- [5] Boveri, T. *Ergebnisse Über Die Konstitution Der Chromatischen Substanz Des Zellkerns* (G. Fischer, Jena, 1904).
- [6] Dahm, R. From discovering to understanding. Friedrich Miescher's attempts to uncover the function of DNA. *EMBO Rep* **11**, 153–60 (2010).
- [7] Watson, J. D. & Crick, F. H. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* **171**, 737–8 (1953).
- [8] Sanger, F., Coulson, A. R., Hong, G. F., Hill, D. F. & Petersen, G. B. Nucleotide sequence of bacteriophage lambda DNA. *J Mol Biol* **162**, 729–73 (1982).
- [9] Sanger, F. *et al.* Nucleotide sequence of bacteriophage phi X174 DNA. *Nature* **265**, 687–95 (1977).
- [10] Fiers, W. *et al.* Complete nucleotide sequence of SV40 DNA. *Nature* **273**, 113–20 (1978).
- [11] Anderson, S. *et al.* Sequence and organization of the human mitochondrial genome. *Nature* **290**, 457–65 (1981).

- [12] Lander, E. S. *et al.* Initial sequencing and analysis of the human genome. *Nature* **409**, 860–921 (2001).
- [13] International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. *Nature* **431**, 931–45 (2004).
- [14] Mardis, E. R. A decade's perspective on DNA sequencing technology. *Nature* **470**, 198–203 (2011).
- [15] The 1000 Genomes Project Consortium *et al.* An integrated map of genetic variation from 1,092 human genomes. *Nature* **491**, 56–65 (2012).
- [16] Kaye, J. *et al.* Managing clinically significant findings in research: the UK10K example. *Eur J Hum Genet* (2014).
- [17] Fu, W. *et al.* Analysis of 6,515 exomes reveals the recent origin of most human protein-coding variants. *Nature* **493**, 216–20 (2013).
- [18] Encode Project Consortium *et al.* An integrated encyclopedia of DNA elements in the human genome. *Nature* **489**, 57–74 (2012).
- [19] Bernstein, B. E. *et al.* The NIH Roadmap Epigenomics Mapping Consortium. *Nat Biotechnol* **28**, 1045–8 (2010).
- [20] Adams, D. *et al.* BLUEPRINT to decode the epigenetic signature written in blood. *Nat Biotechnol* **30**, 224–6 (2012).
- [21] Ford, C. E. & Hamerton, J. L. The chromosomes of man. *Nature* **178**, 1020–3 (1956).
- [22] Tjio, J. H. & Levan, A. The Chromosome Number of Man. *Hereditas* **42**, 1–6 (1956).
- [23] Gersen, S. & Keagle, M. *The Principles of Clinical Cytogenetics* (Humana Press, 2008).
- [24] Morton, N. E. Parameters of the human genome. *Proc Natl Acad Sci U S A* **88**, 7474–6 (1991).
- [25] Fields, C., Adams, M. D., White, O. & Venter, J. C. How many genes in the human genome? *Nat Genet* **7**, 345–6 (1994).

- [26] Hillier, L. W. *et al.* Genomics in *C. elegans*: so many genes, such a little worm. *Genome Res* **15**, 1651–60 (2005).
- [27] Carlton, J. M. *et al.* Draft genome sequence of the sexually transmitted pathogen *Trichomonas vaginalis*. *Science* **315**, 207–12 (2007).
- [28] Schnable, P. S. *et al.* The B73 maize genome: complexity, diversity, and dynamics. *Science* **326**, 1112–5 (2009).
- [29] Brenchley, R. *et al.* Analysis of the bread wheat genome using whole-genome shotgun sequencing. *Nature* **491**, 705–10 (2012).
- [30] Pan, Q., Shai, O., Lee, L. J., Frey, B. J. & Blencowe, B. J. Deep surveying of alternative splicing complexity in the human transcriptome by high-throughput sequencing. *Nat Genet* **40**, 1413–5 (2008).
- [31] Stumpf, M. P. *et al.* Estimating the size of the human interactome. *Proc Natl Acad Sci U S A* **105**, 6959–64 (2008).
- [32] Salse, J. *et al.* Identification and characterization of shared duplications between rice and wheat provide new insight into grass genome evolution. *Plant Cell* **20**, 11–24 (2008).
- [33] Jensen, O. N. Interpreting the protein language using proteomics. *Nat Rev Mol Cell Biol* **7**, 391–403 (2006).
- [34] Khan, Z. *et al.* Primate transcript and protein expression levels evolve under compensatory selection pressures. *Science* **342**, 1100–4 (2013).
- [35] Levine, M. & Tjian, R. Transcription regulation and animal diversity. *Nature* **424**, 147–51 (2003).
- [36] Mattick, J. S. RNA regulation: a new genetics? *Nat Rev Genet* **5**, 316–23 (2004).
- [37] Mattick, J. S. Challenging the dogma: the hidden layer of non-protein-coding RNAs in complex organisms. *Bioessays* **25**, 930–9 (2003).
- [38] Encode Project Consortium. The ENCODE (ENCyclopedia Of DNA Elements) Project. *Science* **306**, 636–40 (2004).
- [39] Djebali, S. *et al.* Landscape of transcription in human cells. *Nature* **489**, 101–8 (2012).

- [40] The 1000 Genomes Project Consortium *et al.* A map of human genome variation from population-scale sequencing. *Nature* **467**, 1061–73 (2010).
- [41] Barbujani, G., Ghirotto, S. & Tassi, F. Nine things to remember about human genome diversity. *Tissue Antigens* **82**, 155–64 (2013).
- [42] Macconnail, L. E. & Garraway, L. A. Clinical implications of the cancer genome. *J Clin Oncol* **28**, 5219–28 (2010).
- [43] von Hansemann, D. Ueber asymmetrische Zelltheilung in epithel Krebsen und deren biologische Bedeutung. *Virchows Arch Path Anat* **119**, 299 (1890).
- [44] Mukherjee, S. *The emperor of all maladies : a biography of cancer* (Scribner, New York, 2011), 1st Scribner trade paperback edn.
- [45] Balmain, A. Cancer genetics: from Boveri and Mendel to microarrays. *Nat Rev Cancer* **1**, 77–82 (2001).
- [46] Boveri, T. Uber mehrpolige mitosen als mittel zur analyse des zellkerns. *Verh D Phys Med Ges Wurzberg N F* **35**, 67–70 (1902).
- [47] Loeb, L. A. & Harris, C. C. Advances in chemical carcinogenesis: a historical review and prospective. *Cancer Res* **68**, 6863–72 (2008).
- [48] Yamagiwa, K. & Ichikawa, K. Experimental Study of the Pathogenesis of Carcinoma. *J Cancer Res* **3**, 1–29 (1918).
- [49] Kennaway, E. L. Further experiments on cancer-producing substances. *Biochem J* **24**, 497–504 (1930).
- [50] Balmain, A. & Pragnell, I. B. Mouse skin carcinomas induced *in vivo* by chemical carcinogens have a transforming Harvey-*ras* oncogene. *Nature* **303**, 72–4 (1983).
- [51] Carrell, C. J., Carrell, T. G., Carrell, H. L., Prout, K. & Glusker, J. P. Benzo[*a*]pyrene and its analogues: structural studies of molecular strain. *Carcinogenesis* **18**, 415–22 (1997).
- [52] Croy, R. G., Essigmann, J. M., Reinhold, V. N. & Wogan, G. N. Identification of the principal aflatoxin B<sub>1</sub>-DNA adduct formed *in vivo* in rat liver. *Proc Natl Acad Sci U S A* **75**, 1745–9 (1978).

- [53] Reddy, E. P., Reynolds, R. K., Santos, E. & Barbacid, M. A point mutation is responsible for the acquisition of transforming properties by the T24 human bladder carcinoma oncogene. *Nature* **300**, 149–52 (1982).
- [54] Brown, J. R. & Thornton, J. L. Percivall Pott (1714–1788) and chimney sweepers' cancer of the scrotum. *Br J Ind Med* **14**, 68–70 (1957).
- [55] American Cancer Society. Occupation and Cancer. URL <http://www.cancer.org/acs/groups/content/@nho/documents/document/occupationandcancerpdf.pdf>.
- [56] Boffetta, P. & Nyberg, F. Contribution of environmental factors to cancer risk. *Br Med Bull* **68**, 71–94 (2003).
- [57] Cogliano, V. J. *et al.* Preventable exposures associated with human cancers. *J Natl Cancer Inst* **103**, 1827–39 (2011).
- [58] Hernandez, L. G., van Steeg, H., Luijten, M. & van Benthem, J. Mechanisms of non-genotoxic carcinogens and importance of a weight of evidence approach. *Mutat Res* **682**, 94–109 (2009).
- [59] Liu, G., Cheresh, P. & Kamp, D. W. Molecular basis of asbestos-induced lung disease. *Annu Rev Pathol* **8**, 161–87 (2013).
- [60] Tweedale, G. & Hansen, P. Protecting the workers: the medical board and the asbestos industry, 1930s–1960s. *Med Hist* **42**, 439–57 (1998).
- [61] Luus, K. Asbestos: mining exposure, health effects and policy implications. *Mcgill J Med* **10**, 121–6 (2007).
- [62] Committee on Asbestos: Selected Health Effects, Board on Population Health and Public Health Practice, Institute of Medicine. *Asbestos:: Selected Cancers* (National Academies Press, 2006).
- [63] Kamp, D. W. & Weitzman, S. A. The molecular basis of asbestos induced lung injury. *Thorax* **54**, 638–52 (1999).
- [64] Boffetta, P. Epidemiology of environmental and occupational cancer. *Oncogene* **23**, 6392–403 (2004).
- [65] Newhouse, M. L., Berry, G. & Wagner, J. C. Mortality of factory workers in east London 1933–80. *Br J Ind Med* **42**, 4–11 (1985).

- [66] Case, B. W., Abraham, J. L., Meeker, G., Pooley, F. D. & Pinkerton, K. E. Applying definitions of "asbestos" to environmental and "low-dose" exposure levels and health effects, particularly malignant mesothelioma. *J Toxicol Environ Health B Crit Rev* **14**, 3–39 (2011).
- [67] Cordier, S. *et al.* Epidemiologic investigation of respiratory effects related to environmental exposure to asbestos inside insulated buildings. *Arch Environ Health* **42**, 303–9 (1987).
- [68] Substance Abuse and Mental Health Services Administration (SAMHSA). National Survey on Drug Use and Health (NSDUH). URL <http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/DetTabs/NSDUH-DetTabsSect2peTabs43to84-2012.htm#Tab2.71B>.
- [69] Office for National Statistics. 5 interesting facts about alcohol consumption in Great Britain. URL <http://www.ons.gov.uk/ons/rel/ghs/opinions-and-lifestyle-survey/drinking-habits-amongst-adults--2012/sty-alcohol-consumption.html>.
- [70] Lamu, L. Etude de statistique clinique de 131 cas de cancer de l'oesophage et du cardia. *Archives des Maladies Digestifs et de Malnutrition* **4**, 451–456 (1910).
- [71] Poschl, G. & Seitz, H. K. Alcohol and cancer. *Alcohol Alcohol* **39**, 155–65 (2004).
- [72] International Agency for Research on Cancer. Alcohol Drinking. Tech. Rep. 44, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (1988). URL <http://monographs.iarc.fr/ENG/Monographs/vol44/volume44.pdf>.
- [73] Seitz, H. K. & Stickel, F. Molecular mechanisms of alcohol-mediated carcinogenesis. *Nat Rev Cancer* **7**, 599–612 (2007).
- [74] Brooks, P. J. & Theruvathu, J. A. DNA adducts from acetaldehyde: implications for alcohol-related carcinogenesis. *Alcohol* **35**, 187–93 (2005).
- [75] Travis, R. C. & Key, T. J. Oestrogen exposure and breast cancer risk. *Breast Cancer Res* **5**, 239–47 (2003).
- [76] Lopes, C. F. *et al.* Concomitant consumption of marijuana, alcohol and tobacco in oral squamous cell carcinoma development and progression: recent advances and challenges. *Arch Oral Biol* **57**, 1026–33 (2012).

- [77] Eichner, E. R. & Hillman, R. S. Effect of alcohol on serum folate level. *J Clin Invest* **52**, 584–91 (1973).
- [78] Boffetta, P., Hashibe, M., La Vecchia, C., Zatonski, W. & Rehm, J. The burden of cancer attributable to alcohol drinking. *Int J Cancer* **119**, 884–7 (2006).
- [79] Nelson, D. E. *et al.* Alcohol-attributable cancer deaths and years of potential life lost in the United States. *Am J Public Health* **103**, 641–8 (2013).
- [80] International Agency for Research on Cancer. A Review of Human Carcinogens: Chemical Agents and Related Occupations. Tech. Rep. 100F, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (2012). URL <http://monographs.iarc.fr/ENG/Monographs/vol100F/mono100F-21.pdf>.
- [81] Butlin, H. T. Cancer of the scrotum in chimney sweeps and others. II. Why foreign sweeps do not suffer from scrotal cancer. *British Medical Journal* **2**, 1–6 (1892).
- [82] Poirier, M. C. Chemical-induced DNA damage and human cancer risk. *Nat Rev Cancer* **4**, 630–7 (2004).
- [83] Cook, J. & Kennaway, E. L. Chemical Compounds as Carcinogenic Agents: First Supplementary Report: Literature of 1937. *Cancer Res* **33**, 50–97 (1938).
- [84] Levin, W. *et al.* Carcinogenicity of benzo[a]pyrene 4,5-, 7,8-, and 9,10-oxides on mouse skin. *Proc Natl Acad Sci U S A* **73**, 243–7 (1976).
- [85] Kim, J. H. *et al.* Metabolism of benzo[a]pyrene and benzo[a]pyrene-7,8-diol by human cytochrome P450 1B1. *Carcinogenesis* **19**, 1847–53 (1998).
- [86] Volk, D. E. *et al.* Solution structure of a cis-opened (10R)-N6-deoxyadenosine adduct of (9S,10R)-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene in a DNA duplex. *Biochemistry* **42**, 1410–20 (2003).
- [87] Mao, B. *et al.* Solution structure of the (+)-cis-anti-benzo[a]pyrene-dA ([BP]dA) adduct opposite dT in a DNA duplex. *Biochemistry* **38**, 10831–42 (1999).
- [88] Doll, R. & Hill, A. B. Smoking and carcinoma of the lung; preliminary report. *Br Med J* **2**, 739–48 (1950).
- [89] Witschi, H. A short history of lung cancer. *Toxicol Sci* **64**, 4–6 (2001).

- [90] Wynder, E. L. & Graham, E. A. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma; a study of 684 proved cases. *J Am Med Assoc* **143**, 329–36 (1950).
- [91] International Agency for Research on Cancer. Tobacco Smoke and Involuntary Smoking. Tech. Rep. 83, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (2004). URL <http://monographs.iarc.fr/ENG/Monographs/vol83/mono83-6C.pdf>.
- [92] Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US). *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Chapter 5: Cancer* (Centers for Disease Control and Prevention (US), 2010). URL <http://www.ncbi.nlm.nih.gov/books/NBK53010/>.
- [93] Feng, Z. *et al.* Preferential DNA damage and poor repair determine *ras* gene mutational hotspot in human cancer. *J Natl Cancer Inst* **94**, 1527–36 (2002).
- [94] Tang, M. S., Zheng, J. B., Denissenko, M. F., Pfeifer, G. P. & Zheng, Y. Use of UvrABC nuclease to quantify benzo[a]pyrene diol epoxide-DNA adduct formation at methylated versus unmethylated CpG sites in the p53 gene. *Carcinogenesis* **20**, 1085–9 (1999).
- [95] Sasco, A. J., Secretan, M. B. & Straif, K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. *Lung Cancer* **45 Suppl 2**, S3–9 (2004).
- [96] Goel, S., Ravindra, K., Singh, R. J. & Sharma, D. Effective smoke-free policies in achieving a high level of compliance with smoke-free law: experiences from a district of North India. *Tob Control* (2013).
- [97] Kostova, D. *et al.* Cigarette prices and smoking prevalence after a tobacco tax increase - Turkey, 2008 and 2012. *MMWR Morb Mortal Wkly Rep* **63**, 457–61 (2014).
- [98] Abascal, W. *et al.* Tobacco control campaign in Uruguay: a population-based trend analysis. *Lancet* **380**, 1575–82 (2012).

- [99] McAfee, T., Davis, K. C., Alexander, J., R. L., Pechacek, T. F. & Bunnell, R. Effect of the first federally funded US antismoking national media campaign. *Lancet* **382**, 2003–11 (2013).
- [100] de Gruyl, F. R. Skin cancer and solar UV radiation. *Eur J Cancer* **35**, 2003–9 (1999).
- [101] MacKie, R. M. *Skin cancer : an illustrated guide to the aetiology, clinical features, pathology and management of benign and malignant cutaneous tumours.* Focal points in dermatology (M. Dunitz ; Year Book Medical Publishers, London Chicago, 1989).
- [102] International Agency for Research on Cancer. Solar and Ultraviolet Radiation. Tech. Rep. 55, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (1992). URL <http://monographs.iarc.fr/ENG/Monographs/vol100F/mono100F-21.pdf>.
- [103] Young, C. Solar ultraviolet radiation and skin cancer. *Occup Med (Lond)* **59**, 82–8 (2009).
- [104] Taylor, J. S. Unraveling the Molecular Pathway from Sunlight to Skin Cancer. *Accounts of Chemical Research* **27**, 76–82 (1994).
- [105] Devary, Y., Rosette, C., DiDonato, J. A. & Karin, M. NF-kappa B activation by ultraviolet light not dependent on a nuclear signal. *Science* **261**, 1442–5 (1993).
- [106] Chen, A. C., Halliday, G. M. & Damian, D. L. Non-melanoma skin cancer: carcinogenesis and chemoprevention. *Pathology* **45**, 331–41 (2013).
- [107] Brash, D. E. Sunlight and the onset of skin cancer. *Trends Genet* **13**, 410–4 (1997).
- [108] Ikehata, H. & Ono, T. The mechanisms of UV mutagenesis. *J Radiat Res* **52**, 115–25 (2011).
- [109] Nelson, D. L. & Cox, M. M. *Lehninger Principles of Biochemistry* (W.H. Freeman and Company, 2013), 6th edn.
- [110] Parkin, D. M., Mesher, D. & Sasieni, P. 13. Cancers attributable to solar (ultraviolet) radiation exposure in the UK in 2010. *Br J Cancer* **105 Suppl 2**, S66–9 (2011).

- [111] de Vries, E. & Coebergh, J. W. Cutaneous malignant melanoma in Europe. *Eur J Cancer* **40**, 2355–66 (2004).
- [112] Diffey, B. L. & Norridge, Z. Reported sun exposure, attitudes to sun protection and perceptions of skin cancer risk: a survey of visitors to Cancer Research UK's SunSmart campaign website. *Br J Dermatol* **160**, 1292–8 (2009).
- [113] Makin, J. K., Warne, C. D., Dobbins, S. J., Wakefield, M. A. & Hill, D. J. Population and age-group trends in weekend sun protection and sunburn over two decades of the SunSmart programme in Melbourne, Australia. *Br J Dermatol* **168**, 154–61 (2013).
- [114] Reeder, A. I., Jopson, J. A. & Gray, A. Baseline survey of sun protection policies and practices in primary school settings in New Zealand. *Health Educ Res* **24**, 778–87 (2009).
- [115] Devesa, S. S., Blot, W. J. & Fraumeni, J., J. F. Declining lung cancer rates among young men and women in the United States: a cohort analysis. *J Natl Cancer Inst* **81**, 1568–71 (1989).
- [116] Polednak, A. P. Tobacco control indicators and lung cancer rates in young adults by state in the United States. *Tob Control* **17**, 66–9 (2008).
- [117] Klauber-DeMore, N. *Breast cancer in young women* (IOS Press, Amsterdam ; Washington, DC, 2006), Breast disease book edn.
- [118] Warthin, A. Heredity with reference to carcinoma. *Arch Intern Med (Chic)* **XII(5)**, 546–555 (1913).
- [119] Douglas, J. A. *et al.* History and molecular genetics of Lynch syndrome in family G: a century later. *JAMA* **294**, 2195–202 (2005).
- [120] Lynch, H. T. Classics in oncology. Aldred Scott Warthin, M.D., Ph.D. (1866-1931). *CA Cancer J Clin* **35**, 345–7 (1985).
- [121] Hansen, M. F. & Cavenee, W. K. Genetics of cancer predisposition. *Cancer Res* **47**, 5518–27 (1987).
- [122] Fletcher, O. & Houlston, R. S. Architecture of inherited susceptibility to common cancer. *Nat Rev Cancer* **10**, 353–61 (2010).

- [123] Balmain, A., Gray, J. & Ponder, B. The genetics and genomics of cancer. *Nat Genet* **33 Suppl**, 238–44 (2003).
- [124] Schimke, R. N. Genetic aspects of multiple endocrine neoplasia. *Annu Rev Med* **35**, 25–31 (1984).
- [125] Sparkes, R. S. *et al.* Gene for hereditary retinoblastoma assigned to human chromosome 13 by linkage to esterase D. *Science* **219**, 971–3 (1983).
- [126] Strong, L. C., Riccardi, V. M., Ferrell, R. E. & Sparkes, R. S. Familial retinoblastoma and chromosome 13 deletion transmitted via an insertional translocation. *Science* **213**, 1501–3 (1981).
- [127] Knudson, J., A. G. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A* **68**, 820–3 (1971).
- [128] Friend, S. H. *et al.* A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. *Nature* **323**, 643–6 (1986).
- [129] Rahman, N. Realizing the promise of cancer predisposition genes. *Nature* **505**, 302–8 (2014).
- [130] Hall, J. M. *et al.* Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* **250**, 1684–9 (1990).
- [131] Miki, Y. *et al.* A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. *Science* **266**, 66–71 (1994).
- [132] Nagy, R., Sweet, K. & Eng, C. Highly penetrant hereditary cancer syndromes. *Oncogene* **23**, 6445–70 (2004).
- [133] Fearon, E. R. Human cancer syndromes: clues to the origin and nature of cancer. *Science* **278**, 1043–50 (1997).
- [134] Chang, C. Q. *et al.* A systematic review of cancer GWAS and candidate gene meta-analyses reveals limited overlap but similar effect sizes. *Eur J Hum Genet* **22**, 402–8 (2014).
- [135] Frank, S. A. Genetic predisposition to cancer - insights from population genetics. *Nat Rev Genet* **5**, 764–72 (2004).

- [136] Marsh, D. & Zori, R. Genetic insights into familial cancers— update and recent discoveries. *Cancer Lett* **181**, 125–64 (2002).
- [137] Vogel, F. Genetics of retinoblastoma. *Hum Genet* **52**, 1–54 (1979).
- [138] Classon, M. & Harlow, E. The retinoblastoma tumour suppressor in development and cancer. *Nat Rev Cancer* **2**, 910–7 (2002).
- [139] DeCaprio, J. A. *et al.* SV40 large tumor antigen forms a specific complex with the product of the retinoblastoma susceptibility gene. *Cell* **54**, 275–83 (1988).
- [140] Whyte, P. *et al.* Association between an oncogene and an anti-oncogene: the adenovirus E1A proteins bind to the retinoblastoma gene product. *Nature* **334**, 124–9 (1988).
- [141] Henley, S. A. & Dick, F. A. The retinoblastoma family of proteins and their regulatory functions in the mammalian cell division cycle. *Cell Div* **7**, 10 (2012).
- [142] Broaddus, E., Topham, A. & Singh, A. D. Incidence of retinoblastoma in the USA: 1975–2004. *Br J Ophthalmol* **93**, 21–3 (2009).
- [143] Valverde, J. R., Alonso, J., Palacios, I. & Pestaña, A. *RB1* gene mutation update, a meta-analysis based on 932 reported mutations available in a searchable database. *BMC Genet* **6**, 53 (2005).
- [144] Dommering, C. J. *et al.* *RB1* mutation spectrum in a comprehensive nationwide cohort of retinoblastoma patients. *J Med Genet* **51**, 366–74 (2014).
- [145] Szijan, I., Lohmann, D. R., Parma, D. L., Brandt, B. & Horsthemke, B. Identification of *RB1* germline mutations in Argentinian families with sporadic bilateral retinoblastoma. *J Med Genet* **32**, 475–9 (1995).
- [146] Harding, F. *Breast cancer: cause, prevention, cure* (Tekline Pub., Aylesbury, 2006).
- [147] Sudhakar, A. History of Cancer, Ancient and Modern Treatment Methods. *J Cancer Sci Ther* **1**, 1–4 (2009).
- [148] Bray, F., Ren, J.-S., Masuyer, E. & Ferlay, J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer* **132**, 1133–45 (2013).

- [149] Wooster, R. *et al.* Identification of the breast cancer susceptibility gene *BRCA2*. *Nature* **378**, 789–92 (1995).
- [150] Ford, D. *et al.* Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* **62**, 676–89 (1998).
- [151] Chen, S. & Parmigiani, G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. *J Clin Oncol* **25**, 1329–33 (2007).
- [152] Venkitaraman, A. R. Functions of *BRCA1* and *BRCA2* in the biological response to DNA damage. *J Cell Sci* **114**, 3591–8 (2001).
- [153] Yoshida, K. & Miki, Y. Role of *BRCA1* and *BRCA2* as regulators of DNA repair, transcription, and cell cycle in response to DNA damage. *Cancer Sci* **95**, 866–71 (2004).
- [154] Gardini, A., Baillat, D., Cesaroni, M. & Shiekhattar, R. Genome-wide analysis reveals a role for *BRCA1* and *PALB2* in transcriptional co-activation. *EMBO J* **33**, 890–905 (2014).
- [155] Konishi, H. *et al.* Mutation of a single allele of the cancer susceptibility gene *BRCA1* leads to genomic instability in human breast epithelial cells. *Proc Natl Acad Sci U S A* **108**, 17773–8 (2011).
- [156] Yata, K. *et al.* BRCA2 Coordinates the Activities of Cell-Cycle Kinases to Promote Genome Stability. *Cell Rep* (2014).
- [157] Connor, F. *et al.* Tumorigenesis and a DNA repair defect in mice with a truncating *Brc2* mutation. *Nat Genet* **17**, 423–30 (1997).
- [158] Collins, N. *et al.* Consistent loss of the wild type allele in breast cancers from a family linked to the *BRCA2* gene on chromosome 13q12-13. *Oncogene* **10**, 1673–5 (1995).
- [159] Staff, S., Nupponen, N. N., Borg, A., Isola, J. J. & Tanner, M. M. Multiple copies of mutant *BRCA1* and *BRCA2* alleles in breast tumors from germ-line mutation carriers. *Genes Chromosomes Cancer* **28**, 432–42 (2000).

- [160] Thompson, E. R. *et al.* Exome sequencing identifies rare deleterious mutations in DNA repair genes *FANCC* and *BLM* as potential breast cancer susceptibility alleles. *PLoS Genet* **8**, e1002894 (2012).
- [161] Easton, D. F. & Eeles, R. A. Genome-wide association studies in cancer. *Hum Mol Genet* **17**, R109–15 (2008).
- [162] Rodriguez-Bigas, M. A. *Hereditary colorectal cancer*. M.D. Anderson solid tumor oncology series (Springer, New York, 2010).
- [163] Yan, H. *et al.* Conversion of diploidy to haploidy. *Nature* **403**, 723–4 (2000).
- [164] Silva, F. C. C. d., Valentin, M. D., Ferreira, F. d. O., Carraro, D. M. & Rossi, B. M. Mismatch repair genes in Lynch syndrome: a review. *Sao Paulo Med J* **127**, 46–51 (2009).
- [165] Nagasaka, T. *et al.* Somatic hypermethylation of *MSH2* is a frequent event in Lynch Syndrome colorectal cancers. *Cancer Res* **70**, 3098–108 (2010).
- [166] Bodmer, W. F. *et al.* Localization of the gene for familial adenomatous polyposis on chromosome 5. *Nature* **328**, 614–6 (1987).
- [167] Powell, S. M. *et al.* *APC* mutations occur early during colorectal tumorigenesis. *Nature* **359**, 235–7 (1992).
- [168] Kinzler, K. W. & Vogelstein, B. Lessons from hereditary colorectal cancer. *Cell* **87**, 159–70 (1996).
- [169] Fearon, E. R. Molecular genetics of colorectal cancer. *Annu Rev Pathol* **6**, 479–507 (2011).
- [170] Li, F. P. & Fraumeni, J. F., Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? *Ann Intern Med* **71**, 747–52 (1969).
- [171] Malkin, D. *et al.* Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* **250**, 1233–8 (1990).
- [172] Srivastava, S., Zou, Z. Q., Pirollo, K., Blattner, W. & Chang, E. H. Germ-line transmission of a mutated *p53* gene in a cancer-prone family with Li-Fraumeni syndrome. *Nature* **348**, 747–9 (1990).

- [173] Malkin, D. Li-fraumeni syndrome. *Genes Cancer* **2**, 475–84 (2011).
- [174] Sedlacek, Z. *et al.* Two Li-Fraumeni syndrome families with novel germline *p53* mutations: loss of the wild-type *p53* allele in only 50% of tumours. *Br J Cancer* **77**, 1034–9 (1998).
- [175] Vogelstein, B., Lane, D. & Levine, A. J. Surfing the *p53* network. *Nature* **408**, 307–10 (2000).
- [176] Efeyan, A. & Serrano, M. *p53*: guardian of the genome and policeman of the oncogenes. *Cell Cycle* **6**, 1006–10 (2007).
- [177] Walls, G. V. Multiple endocrine neoplasia (MEN) syndromes. *Semin Pediatr Surg* **23**, 96–101 (2014).
- [178] Wells, S. A., Jr, Pacini, F., Robinson, B. G. & Santoro, M. Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma: an update. *J Clin Endocrinol Metab* **98**, 3149–64 (2013).
- [179] Donis-Keller, H. *et al.* Mutations in the *RET* proto-oncogene are associated with MEN 2A and FMTC. *Hum Mol Genet* **2**, 851–6 (1993).
- [180] Mulligan, L. M. *et al.* Germ-line mutations of the *RET* proto-oncogene in multiple endocrine neoplasia type 2A. *Nature* **363**, 458–60 (1993).
- [181] Hofstra, R. M. *et al.* A mutation in the *RET* proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. *Nature* **367**, 375–6 (1994).
- [182] Mulligan, L. M. *RET* revisited: expanding the oncogenic portfolio. *Nat Rev Cancer* **14**, 173–86 (2014).
- [183] Besset, V., Scott, R. P. & Ibáñez, C. F. Signaling complexes and protein-protein interactions involved in the activation of the Ras and phosphatidylinositol 3-kinase pathways by the c-Ret receptor tyrosine kinase. *J Biol Chem* **275**, 39159–66 (2000).
- [184] Davenport, M. P., Ward, R. L. & Hawkins, N. J. The null oncogene hypothesis and protection from cancer. *J Med Genet* **39**, 12–4 (2002).
- [185] Chin, L. The genetics of malignant melanoma: lessons from mouse and man. *Nat Rev Cancer* **3**, 559–70 (2003).

- [186] Kamb, A. *et al.* A cell cycle regulator potentially involved in genesis of many tumor types. *Science* **264**, 436–40 (1994).
- [187] Spruck, C. H., 3rd *et al.* p16 gene in uncultured tumours. *Nature* **370**, 183–4 (1994).
- [188] Cannon-Albright, L. A. *et al.* Assignment of a locus for familial melanoma, MLM, to chromosome 9p13-p22. *Science* **258**, 1148–52 (1992).
- [189] Cairns, P. *et al.* Frequency of homozygous deletion at *p16/CDKN2* in primary human tumours. *Nat Genet* **11**, 210–2 (1995).
- [190] Gruis, N. A. *et al.* Homozygotes for *CDKN2* (p16) germline mutation in Dutch familial melanoma kindreds. *Nat Genet* **10**, 351–3 (1995).
- [191] Liggett, W. H., Jr & Sidransky, D. Role of the p16 tumor suppressor gene in cancer. *J Clin Oncol* **16**, 1197–206 (1998).
- [192] Hussussian, C. J. *et al.* Germline p16 mutations in familial melanoma. *Nat Genet* **8**, 15–21 (1994).
- [193] Ranade, K. *et al.* Mutations associated with familial melanoma impair p16INK4 function. *Nat Genet* **10**, 114–6 (1995).
- [194] Hayward, N. K. Genetics of melanoma predisposition. *Oncogene* **22**, 3053–62 (2003).
- [195] de Snoo, F. A. & Hayward, N. K. Cutaneous melanoma susceptibility and progression genes. *Cancer Lett* **230**, 153–86 (2005).
- [196] Randerson-Moor, J. A. *et al.* A germline deletion of p14(ARF) but not *CDKN2A* in a melanoma-neural system tumour syndrome family. *Hum Mol Genet* **10**, 55–62 (2001).
- [197] Rizos, H. *et al.* A melanoma-associated germline mutation in exon 1beta inactivates p14ARF. *Oncogene* **20**, 5543–7 (2001).
- [198] Flores, J. F. *et al.* Analysis of the *CDKN2A*, *CDKN2B* and *CDK4* genes in 48 Australian melanoma kindreds. *Oncogene* **15**, 2999–3005 (1997).
- [199] Zuo, L. *et al.* Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. *Nat Genet* **12**, 97–9 (1996).

- [200] Kong, C. M., Lee, X. W. & Wang, X. Telomere shortening in human diseases. *FEBS J* **280**, 3180–93 (2013).
- [201] Pharoah, P. D. P. *et al.* Polygenic susceptibility to breast cancer and implications for prevention. *Nat Genet* **31**, 33–6 (2002).
- [202] American Cancer Society. Cancer facts & figures (2014). URL <http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf>.
- [203] Cancer Research UK. Skin cancer incidence statistics. URL <http://www.cancerresearchuk.org/cancer-info/cancerstats/types/skin/incidence/uk-skin-cancer-incidence-statistics>.
- [204] Rahib, L. *et al.* Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* **74**, 2913–21 (2014).
- [205] Cancer Research UK. Cancer incidence for common cancers (2014). URL <http://www.cancerresearchuk.org/cancer-info/cancerstats/incidence/commoncancers/uk-cancer-incidence-statistics-for-common-cancers>.
- [206] Iannacone, M. R., Youlden, D. R., Baade, P. D., Aitken, J. F. & Green, A. C. Melanoma incidence trends and survival in adolescents and young adults in Queensland, Australia. *Int J Cancer* (2014).
- [207] Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Statistics Review 1975–2010. 5-Year relative survival for the top 5 cancer sites by age, all races, both sexes. URL [http://seer.cancer.gov/csr/1975\\_2010/browse\\_csr.php?sectionSEL=32&pageSEL=sect\\_32\\_table.20.html](http://seer.cancer.gov/csr/1975_2010/browse_csr.php?sectionSEL=32&pageSEL=sect_32_table.20.html).
- [208] Coates, A. S. Systemic chemotherapy for malignant melanoma. *World J Surg* **16**, 277–81 (1992).
- [209] Tsao, H., Chin, L., Garraway, L. A. & Fisher, D. E. Melanoma: from mutations to medicine. *Genes Dev* **26**, 1131–55 (2012).
- [210] Sauka-Spengler, T. & Bronner-Fraser, M. A gene regulatory network orchestrates neural crest formation. *Nat Rev Mol Cell Biol* **9**, 557–68 (2008).

- [211] Colombo, S., Berlin, I., Delmas, V. & Larue, L. *Classical and Nonclassical Melanocytes in Vertebrates*, chap. 2, 21–61. Melanins and Melanosomes (Wiley-VCH Verlag GmbH & Co. KGaA, 2011).
- [212] Uong, A. & Zon, L. I. Melanocytes in development and cancer. *J Cell Physiol* **222**, 38–41 (2010).
- [213] Lemke, G. *Developmental neurobiology* (Elsevier, Academic Press, London, 2009).
- [214] Thomas, A. J. & Erickson, C. A. The making of a melanocyte: the specification of melanoblasts from the neural crest. *Pigment Cell Melanoma Res* **21**, 598–610 (2008).
- [215] Bertolotto, C. Melanoma: from melanocyte to genetic alterations and clinical options. *Scientifica (Cairo)* **2013**, 635203 (2013).
- [216] Gammill, L. S. & Bronner-Fraser, M. Neural crest specification: migrating into genomics. *Nat Rev Neurosci* **4**, 795–805 (2003).
- [217] Bondurand, N. *et al.* Interaction among *SOX10*, *PAX3* and *MITF*, three genes altered in Waardenburg syndrome. *Hum Mol Genet* **9**, 1907–17 (2000).
- [218] Hou, L., Panthier, J. J. & Arnheiter, H. Signaling and transcriptional regulation in the neural crest-derived melanocyte lineage: interactions between KIT and MITF. *Development* **127**, 5379–89 (2000).
- [219] Lin, J. Y. & Fisher, D. E. Melanocyte biology and skin pigmentation. *Nature* **445**, 843–50 (2007).
- [220] Slominski, A. Neuroendocrine activity of the melanocyte. *Exp Dermatol* **18**, 760–3 (2009).
- [221] Le Poole, I. C. *et al.* A novel, antigen-presenting function of melanocytes and its possible relationship to hypopigmentary disorders. *J Immunol* **151**, 7284–92 (1993).
- [222] Costin, G.-E. & Hearing, V. J. Human skin pigmentation: melanocytes modulate skin color in response to stress. *FASEB J* **21**, 976–94 (2007).
- [223] Nestle, F. O., Di Meglio, P., Qin, J.-Z. & Nickoloff, B. J. Skin immune sentinels in health and disease. *Nat Rev Immunol* **9**, 679–91 (2009).

- [224] Plonka, P. M. *et al.* What are melanocytes really doing all day long...? *Exp Dermatol* **18**, 799–819 (2009).
- [225] Cichorek, M., Wachulska, M., Stasiewicz, A. & Tymińska, A. Skin melanocytes: biology and development. *Postepy Dermatol Alergol* **30**, 30–41 (2013).
- [226] Tolleson, W. H. Human melanocyte biology, toxicology, and pathology. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* **23**, 105–61 (2005).
- [227] Mjaatvedt, C. H., Kern, C. B., Norris, R. A., Fairey, S. & Cave, C. L. Normal distribution of melanocytes in the mouse heart. *Anat Rec A Discov Mol Cell Evol Biol* **285**, 748–57 (2005).
- [228] Yajima, I. & Larue, L. The location of heart melanocytes is specified and the level of pigmentation in the heart may correlate with coat color. *Pigment Cell Melanoma Res* **21**, 471–6 (2008).
- [229] Goldgeier, M. H., Klein, L. E., Klein-Angerer, S., Moellmann, G. & Nordlund, J. J. The distribution of melanocytes in the leptomeninges of the human brain. *J Invest Dermatol* **82**, 235–8 (1984).
- [230] Shosuke, I., Wakamatsu, K., d'Ischia, M., Napolitano, A. & Pezzella, A. *Structure of Melanins*, chap. 2, 167–185. Melanins and Melanosomes (Wiley-VCH Verlag GmbH I& Co. KGaA, 2011).
- [231] Wenczl, E. *et al.* (Pheo)melanin photosensitizes UVA-induced DNA damage in cultured human melanocytes. *J Invest Dermatol* **111**, 678–82 (1998).
- [232] Fedorow, H. *et al.* Neuromelanin in human dopamine neurons: comparison with peripheral melanins and relevance to Parkinson's disease. *Prog Neurobiol* **75**, 109–24 (2005).
- [233] Delevoye, C., Giordano, F., Marks, M. & Raposo, G. *Biogenesis of Melanosomes*, chap. 9, 247–294. Melanins and Melanosomes (Wiley-VCH Verlag GmbH & Co. KGaA, 2011).
- [234] Hearing, V. J. Biogenesis of pigment granules: a sensitive way to regulate melanocyte function. *J Dermatol Sci* **37**, 3–14 (2005).
- [235] Marks, M. S. & Seabra, M. C. The melanosome: membrane dynamics in black and white. *Nat Rev Mol Cell Biol* **2**, 738–48 (2001).

- [236] García-Borrón, J. & Olivares Sánchez, M. *Biosynthesis of Melanins*, chap. 4, 87–116. Melanins and Melanosomes (Wiley-VCH Verlag GmbH & Co. KGaA, 2011).
- [237] Chakraborty, A. K. *et al.* Production and release of proopiomelanocortin (POMC) derived peptides by human melanocytes and keratinocytes in culture: regulation by ultraviolet B. *Biochim Biophys Acta* **1313**, 130–8 (1996).
- [238] Kippenberger, S. *et al.* Melanocytes respond to mechanical stretch by activation of mitogen-activated protein kinases (MAPK). *Pigment Cell Res* **13**, 278–80 (2000).
- [239] Berridge, M. J. Cell Signaling Biology (2012). URL <http://www.biochemj.org/csb/007/csb007.pdf>.
- [240] Gupta, P. B. *et al.* The melanocyte differentiation program predisposes to metastasis after neoplastic transformation. *Nat Genet* **37**, 1047–54 (2005).
- [241] Peinado, H., Olmeda, D. & Cano, A. Snail, Zeb and bHLH factors in tumour progression: an alliance against the epithelial phenotype? *Nat Rev Cancer* **7**, 415–28 (2007).
- [242] Bailey, C. M., Morrison, J. A. & Kulesa, P. M. Melanoma revives an embryonic migration program to promote plasticity and invasion. *Pigment Cell Melanoma Res* **25**, 573–83 (2012).
- [243] Seong, I. *et al.* Sox10 controls migration of B16F10 melanoma cells through multiple regulatory target genes. *PLoS One* **7**, e31477 (2012).
- [244] Serrone, L., Zeuli, M., Sega, F. M. & Cognetti, F. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. *J Exp Clin Cancer Res* **19**, 21–34 (2000).
- [245] Quirbt, I. *et al.* Temozolomide for the treatment of metastatic melanoma. *Curr Oncol* **14**, 27–33 (2007).
- [246] Legha, S. S. *et al.* Treatment of metastatic melanoma with combined chemotherapy containing cisplatin, vinblastine and dacarbazine (CVD) and biotherapy using interleukin-2 and interferon-alpha. *Ann Oncol* **7**, 827–35 (1996).
- [247] Marchesi, F. *et al.* Triazene compounds: mechanism of action and related DNA repair systems. *Pharmacol Res* **56**, 275–87 (2007).

- [248] Swift, L. H. & Golsteyn, R. M. Genotoxic anti-cancer agents and their relationship to DNA damage, mitosis, and checkpoint adaptation in proliferating cancer cells. *Int J Mol Sci* **15**, 3403–31 (2014).
- [249] Soengas, M. S. & Lowe, S. W. Apoptosis and melanoma chemoresistance. *Oncogene* **22**, 3138–51 (2003).
- [250] Castillo Arias, J. & Galvonas Jasulionis, M. *Melanoma: Treatments and Resistance*, chap. 16, 439–473. Melanoma - From Early Detection to Treatment (InTech, 2013).
- [251] Bhatia, S., Tykodi, S. S. & Thompson, J. A. Treatment of metastatic melanoma: an overview. *Oncology (Williston Park)* **23**, 488–96 (2009).
- [252] Longo, C. *et al.* De novo melanoma and melanoma arising from pre-existing nevus: in vivo morphologic differences as evaluated by confocal microscopy. *J Am Acad Dermatol* **65**, 604–14 (2011).
- [253] Clark, W. H., Jr *et al.* A study of tumor progression: the precursor lesions of superficial spreading and nodular melanoma. *Hum Pathol* **15**, 1147–65 (1984).
- [254] Pollock, P. M. *et al.* High frequency of *BRAF* mutations in nevi. *Nat Genet* **33**, 19–20 (2003).
- [255] Poynter, J. N. *et al.* *BRAF* and *NRAS* mutations in melanoma and melanocytic nevi. *Melanoma Res* **16**, 267–73 (2006).
- [256] Michaloglou, C. *et al.* *BRAF<sup>E600</sup>*-associated senescence-like cell cycle arrest of human naevi. *Nature* **436**, 720–4 (2005).
- [257] Tsao, H., Mihm, M. C., Jr & Sheehan, C. PTEN expression in normal skin, acquired melanocytic nevi, and cutaneous melanoma. *J Am Acad Dermatol* **49**, 865–72 (2003).
- [258] Miller, A. J. & Mihm, M. C., Jr. Melanoma. *N Engl J Med* **355**, 51–65 (2006).
- [259] Garraway, L. A. *et al.* Integrative genomic analyses identify *MITF* as a lineage survival oncogene amplified in malignant melanoma. *Nature* **436**, 117–22 (2005).
- [260] Levy, C., Khaled, M. & Fisher, D. E. MITF: master regulator of melanocyte development and melanoma oncogene. *Trends Mol Med* **12**, 406–14 (2006).

- [261] Ramirez, R. D. *et al.* Progressive increase in telomerase activity from benign melanocytic conditions to malignant melanoma. *Neoplasia* **1**, 42–9 (1999).
- [262] Guo, H., Carlson, J. A. & Slominski, A. Role of TRPM in melanocytes and melanoma. *Exp Dermatol* **21**, 650–4 (2012).
- [263] Takata, M., Murata, H. & Saida, T. Molecular pathogenesis of malignant melanoma: a different perspective from the studies of melanocytic nevus and acral melanoma. *Pigment Cell Melanoma Res* **23**, 64–71 (2010).
- [264] Kumasaka, M. Y. *et al.* A novel mouse model for *de novo* melanoma. *Cancer Res* **70**, 24–9 (2010).
- [265] Soufir, N. *et al.* Association between endothelin receptor B nonsynonymous variants and melanoma risk. *J Natl Cancer Inst* **97**, 1297–301 (2005).
- [266] Clark, W. H., Goldman, L. I. & Mastrangelo, M. J. *Human malignant melanoma* (Grune & Stratton, New York, 1979).
- [267] Bandarchi, B., Ma, L., Navab, R., Seth, A. & Rasty, G. From melanocyte to metastatic malignant melanoma. *Dermatol Res Pract* **2010** (2010).
- [268] Melanoma Know More. Types of melanoma. URL <http://melanomaknowmore.com/types-of-melanoma/>.
- [269] Menzies, S. W. *Superficial spreading melanoma*, chap. 9a. An Atlas of Dermoscopy (CRC Press, 2004).
- [270] Cohen, L. M. Lentigo maligna and lentigo maligna melanoma. *J Am Acad Dermatol* **33**, 923–36; quiz 937–40 (1995).
- [271] Erkurt, M. A., Aydogdu, I., Kuku, I., Kaya, E. & Basaran, Y. Nodular melanoma presenting with rapid progression and widespread metastases: a case report. *J Med Case Rep* **3**, 50 (2009).
- [272] Chamberlain, A. J., Fritschi, L. & Kelly, J. W. Nodular melanoma: patients' perceptions of presenting features and implications for earlier detection. *J Am Acad Dermatol* **48**, 694–701 (2003).
- [273] Harmelin, E. S., Holcombe, R. N., Goggin, J. P., Carbonell, J. & Wellens, T. Acral lentiginous melanoma. *J Foot Ankle Surg* **37**, 540–5 (1998).

- [274] Coleman, W. P., 3rd, Loria, P. R., Reed, R. J. & Krementz, E. T. Acral lentiginous melanoma. *Arch Dermatol* **116**, 773–6 (1980).
- [275] World Health Organisation Classification of Tumours. *Pathology & Genetics: Skin tumours*, chap. 2 (IARC Press, 2006).
- [276] Curtin, J. A. *et al.* Distinct sets of genetic alterations in melanoma. *N Engl J Med* **353**, 2135–47 (2005).
- [277] Clark, W. H., Jr, From, L., Bernardino, E. A. & Mihm, M. C. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. *Cancer Res* **29**, 705–27 (1969).
- [278] Balch, C. M. *et al.* Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol* **19**, 3635–48 (2001).
- [279] Balch, C. M. *et al.* Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* **27**, 6199–206 (2009).
- [280] Breslow, A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* **172**, 902–8 (1970).
- [281] Friedman, R. J., Rigel, D. S. & Kopf, A. W. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. *CA Cancer J Clin* **35**, 130–51 (1985).
- [282] Abbasi, N. R. *et al.* Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. *JAMA* **292**, 2771–6 (2004).
- [283] Nachbar, F. *et al.* The ABCD rule of dermatoscopy. High prospective value in the diagnosis of doubtful melanocytic skin lesions. *J Am Acad Dermatol* **30**, 551–9 (1994).
- [284] Thomas, L. *et al.* Semiological value of ABCDE criteria in the diagnosis of cutaneous pigmented tumors. *Dermatology* **197**, 11–7 (1998).
- [285] Davies, H. *et al.* Mutations of the *BRAF* gene in human cancer. *Nature* **417**, 949–54 (2002).
- [286] Ball, N. J. *et al.* *RAS* mutations in human melanoma: a marker of malignant progression. *J Invest Dermatol* **102**, 285–90 (1994).

- [287] Hodis, E. *et al.* A landscape of driver mutations in melanoma. *Cell* **150**, 251–63 (2012).
- [288] Alexandrov, L. B. *et al.* Signatures of mutational processes in human cancer. *Nature* **500**, 415–21 (2013).
- [289] Lawrence, M. S. *et al.* Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature* **499**, 214–8 (2013).
- [290] Prickett, T. D. *et al.* Exon capture analysis of G protein-coupled receptors identifies activating mutations in *GRM3* in melanoma. *Nat Genet* **43**, 1119–26 (2011).
- [291] Nikolaev, S. I. *et al.* Exome sequencing identifies recurrent somatic *MAP2K1* and *MAP2K2* mutations in melanoma. *Nat Genet* **44**, 133–9 (2012).
- [292] Prickett, T. D. *et al.* Analysis of the tyrosine kinase in melanoma reveals recurrent mutations in *ERBB4*. *Nat Genet* **41**, 1127–32 (2009).
- [293] Stark, M. S. *et al.* Frequent somatic mutations in *MAP3K5* and *MAP3K9* in metastatic melanoma identified by exome sequencing. *Nat Genet* **44**, 165–9 (2012).
- [294] Kwong, L. N. & Davies, M. A. Navigating the therapeutic complexity of PI3K pathway inhibition in melanoma. *Clin Cancer Res* **19**, 5310–9 (2013).
- [295] Berger, M. F. *et al.* Melanoma genome sequencing reveals frequent *PREX2* mutations. *Nature* **485**, 502–6 (2012).
- [296] Curtin, J. A., Busam, K., Pinkel, D. & Bastian, B. C. Somatic activation of KIT in distinct subtypes of melanoma. *J Clin Oncol* **24**, 4340–6 (2006).
- [297] Horn, S. *et al.* *TERT* promoter mutations in familial and sporadic melanoma. *Science* **339**, 959–61 (2013).
- [298] Huang, F. W. *et al.* Highly recurrent *TERT* promoter mutations in human melanoma. *Science* **339**, 957–9 (2013).
- [299] Gerami, P. *et al.* Copy number gains in 11q13 and 8q24 [corrected] are highly linked to prognosis in cutaneous malignant melanoma. *J Mol Diagn* **13**, 352–8 (2011).
- [300] Puig-Butilé, J. A. *et al.* Genetic alterations in RAS-regulated pathway in acral lentiginous melanoma. *Exp Dermatol* **22**, 148–50 (2013).

- [301] Krauthammer, M. *et al.* Exome sequencing identifies recurrent somatic *RAC1* mutations in melanoma. *Nat Genet* **44**, 1006–14 (2012).
- [302] Stefansson, B. & Brautigan, D. L. Protein phosphatase PP6 N terminal domain restricts G1 to S phase progression in human cancer cells. *Cell Cycle* **6**, 1386–92 (2007).
- [303] Muthusamy, V. *et al.* Amplification of *CDK4* and *MDM2* in malignant melanoma. *Genes Chromosomes Cancer* **45**, 447–54 (2006).
- [304] Hocker, T. & Tsao, H. Ultraviolet radiation and melanoma: a systematic review and analysis of reported sequence variants. *Hum Mutat* **28**, 578–88 (2007).
- [305] Gartner, J. J. *et al.* Whole-genome sequencing identifies a recurrent functional synonymous mutation in melanoma. *Proc Natl Acad Sci U S A* **110**, 13481–6 (2013).
- [306] Cronin, J. C. *et al.* Frequent mutations in the MITF pathway in melanoma. *Pigment Cell Melanoma Res* **22**, 435–44 (2009).
- [307] Wei, X. *et al.* Exome sequencing identifies *GRIN2A* as frequently mutated in melanoma. *Nat Genet* **43**, 442–6 (2011).
- [308] Takano, T. *et al.* Glutamate release promotes growth of malignant gliomas. *Nat Med* **7**, 1010–5 (2001).
- [309] Gandini, S. *et al.* Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer* **41**, 45–60 (2005).
- [310] Boniol, M., Autier, P., Boyle, P. & Gandini, S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. *BMJ* **345**, e4757 (2012).
- [311] International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review. *Int J Cancer* **120**, 1116–22 (2007).
- [312] El Ghissassi, F. *et al.* A review of human carcinogens—part D: radiation. *Lancet Oncol* **10**, 751–2 (2009).
- [313] Sunbeds (Regulation) Act 2010 (2010).

- [314] Lim, H. W. *et al.* Adverse effects of ultraviolet radiation from the use of indoor tanning equipment: time to ban the tan. *J Am Acad Dermatol* **64**, e51–60 (2011).
- [315] Beane Freeman, L. E., Dennis, L. K., Lynch, C. F., Thorne, P. S. & Just, C. L. Toenail arsenic content and cutaneous melanoma in Iowa. *Am J Epidemiol* **160**, 679–87 (2004).
- [316] Nelemans, P. J. *et al.* Swimming and the risk of cutaneous melanoma. *Melanoma Res* **4**, 281–6 (1994).
- [317] Tynes, T., Klaeboe, L. & Haldorsen, T. Residential and occupational exposure to 50 Hz magnetic fields and malignant melanoma: a population based study. *Occup Environ Med* **60**, 343–7 (2003).
- [318] Nelemans, P. J. *et al.* Melanoma and occupation: results of a case-control study in The Netherlands. *Br J Ind Med* **50**, 642–6 (1993).
- [319] Rees, J. L. Genetics of hair and skin color. *Annu Rev Genet* **37**, 67–90 (2003).
- [320] Schiöth, H. B. *et al.* Loss of function mutations of the human melanocortin 1 receptor are common and are associated with red hair. *Biochem Biophys Res Commun* **260**, 488–91 (1999).
- [321] Mitra, D. *et al.* An ultraviolet-radiation-independent pathway to melanoma carcinogenesis in the red hair/fair skin background. *Nature* **491**, 449–53 (2012).
- [322] Healy, E. *et al.* Melanocortin-1-receptor gene and sun sensitivity in individuals without red hair. *Lancet* **355**, 1072–3 (2000).
- [323] Bastiaens, M. *et al.* The melanocortin-1-receptor gene is the major freckle gene. *Hum Mol Genet* **10**, 1701–8 (2001).
- [324] Youl, P. *et al.* Melanoma in adolescents: a case-control study of risk factors in Queensland, Australia. *Int J Cancer* **98**, 92–8 (2002).
- [325] Bliss, J. M. *et al.* Risk of cutaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case-control studies. The International Melanoma Analysis Group (IMAGE). *Int J Cancer* **62**, 367–76 (1995).

- [326] Guenther, C. A., Tasic, B., Luo, L., Bedell, M. A. & Kingsley, D. M. A molecular basis for classic blond hair color in Europeans. *Nat Genet* **46**, 748–52 (2014).
- [327] Grichnik, J. M., Burch, J. A., Burchette, J. & Shea, C. R. The SCF/KIT pathway plays a critical role in the control of normal human melanocyte homeostasis. *J Invest Dermatol* **111**, 233–8 (1998).
- [328] White, D. & Rabago-Smith, M. Genotype-phenotype associations and human eye color. *J Hum Genet* **56**, 5–7 (2011).
- [329] Ibarrola-Villava, M. *et al.* Genetic analysis of three important genes in pigmentation and melanoma susceptibility: *CDKN2A*, *MC1R* and *HERC2/OCA2*. *Exp Dermatol* **19**, 836–44 (2010).
- [330] Jannet, A.-S. *et al.* Allele variations in the *OCA2* gene (pink-eyed-dilution locus) are associated with genetic susceptibility to melanoma. *Eur J Hum Genet* **13**, 913–20 (2005).
- [331] Gandini, S. *et al.* Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* **41**, 28–44 (2005).
- [332] Duffy, K. & Grossman, D. The dysplastic nevus: from historical perspective to management in the modern era: part I. Historical, histologic, and clinical aspects. *J Am Acad Dermatol* **67**, 1.e1–16; quiz 17–8 (2012).
- [333] Bishop, J. A. *et al.* Genotype/phenotype and penetrance studies in melanoma families with germline CDKN2A mutations. *J Invest Dermatol* **114**, 28–33 (2000).
- [334] Tucker, M. A. *et al.* Risk of melanoma and other cancers in melanoma-prone families. *J Invest Dermatol* **100**, 350S–355S (1993).
- [335] Cancer Research UK. Melanoma risks and causes (2014). URL <http://www.cancerresearchuk.org/about-cancer/type/melanoma/about-melanoma-risks-and-causes>.
- [336] Jensen, P. *et al.* Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol* **40**, 177–86 (1999).
- [337] Kubica, A. W. & Brewer, J. D. Melanoma in immunosuppressed patients. *Mayo Clin Proc* **87**, 991–1003 (2012).

- [338] Bertoni, J. M. *et al.* Increased melanoma risk in Parkinson disease: a prospective clinicopathological study. *Arch Neurol* **67**, 347–52 (2010).
- [339] Lens, M. B. & Newton-Bishop, J. A. An association between cutaneous melanoma and non-Hodgkin's lymphoma: pooled analysis of published data with a review. *Ann Oncol* **16**, 460–5 (2005).
- [340] Travis, L. B., Curtis, R. E., Hankey, B. F. & Fraumeni, J. F., Jr. Second cancers in patients with chronic lymphocytic leukemia. *J Natl Cancer Inst* **84**, 1422–7 (1992).
- [341] Beisland, C., Talleraas, O., Bakke, A. & Norstein, J. Multiple primary malignancies in patients with renal cell carcinoma: a national population-based cohort study. *BJU Int* **97**, 698–702 (2006).
- [342] Washington, K. & McDonagh, D. Secondary tumors of the gastrointestinal tract: surgical pathologic findings and comparison with autopsy survey. *Mod Pathol* **8**, 427–33 (1995).
- [343] Draper, G. J., Sanders, B. M. & Kingston, J. E. Second primary neoplasms in patients with retinoblastoma. *Br J Cancer* **53**, 661–71 (1986).
- [344] Moll, A. C., Imhof, S. M., Bouter, L. M. & Tan, K. E. Second primary tumors in patients with retinoblastoma. A review of the literature. *Ophthalmic Genet* **18**, 27–34 (1997).
- [345] Gandini, S. *et al.* Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* **41**, 2040–59 (2005).
- [346] Ford, D. *et al.* Risk of cutaneous melanoma associated with a family history of the disease. The International Melanoma Analysis Group (IMAGE). *Int J Cancer* **62**, 377–81 (1995).
- [347] Breast Cancer Linkage Consortium. Cancer risks in *BRCA2* mutation carriers. *J Natl Cancer Inst* **91**, 1310–6 (1999).
- [348] Risch, H. A. *et al.* Population *BRCA1* and *BRCA2* mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. *J Natl Cancer Inst* **98**, 1694–706 (2006).

- [349] Manolio, T. A. *et al.* Finding the missing heritability of complex diseases. *Nature* **461**, 747–53 (2009).
- [350] Goldstein, A. M. *et al.* Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. *J Med Genet* **44**, 99–106 (2007).
- [351] Ward, K. A., Lazovich, D. & Hordinsky, M. K. Germline melanoma susceptibility and prognostic genes: a review of the literature. *J Am Acad Dermatol* **67**, 1055–67 (2012).
- [352] Bishop, D. T. *et al.* Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J Natl Cancer Inst* **94**, 894–903 (2002).
- [353] Begg, C. B. *et al.* Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. *J Natl Cancer Inst* **97**, 1507–15 (2005).
- [354] Wiesner, T. *et al.* Germline mutations in *BAP1* predispose to melanocytic tumors. *Nat Genet* **43**, 1018–21 (2011).
- [355] Vinagre, J. *et al.* Frequency of *TERT* promoter mutations in human cancers. *Nat Commun* **4**, 2185 (2013).
- [356] Raimondi, S. *et al.* *MC1R* variants, melanoma and red hair color phenotype: a meta-analysis. *Int J Cancer* **122**, 2753–60 (2008).
- [357] Bertolotto, C. *et al.* A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma. *Nature* **480**, 94–8 (2011).
- [358] Yokoyama, S. *et al.* A novel recurrent mutation in *MITF* predisposes to familial and sporadic melanoma. *Nature* **480**, 99–103 (2011).
- [359] Gudbjartsson, D. F. *et al.* *ASIP* and *TYR* pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. *Nat Genet* **40**, 886–91 (2008).
- [360] Kvaskoff, M. *et al.* Polymorphisms in nevus-associated genes *MTAP*, *PLA2G6*, and *IRF4* and the risk of invasive cutaneous melanoma. *Twin Res Hum Genet* **14**, 422–32 (2011).

- [361] Park, J. Y. *et al.* Gene variants in angiogenesis and lymphangiogenesis and cutaneous melanoma progression. *Cancer Epidemiol Biomarkers Prev* **22**, 827–34 (2013).
- [362] Shahbazi, M. *et al.* Association between functional polymorphism in *EGF* gene and malignant melanoma. *Lancet* **359**, 397–401 (2002).
- [363] Norris, W. A case of fungoid disease. *Edinb. Med. Surg.* **16**, 562–565 (1820).
- [364] Lynch, H. T., Fritchot, B. C., 3rd & Lynch, J. F. Familial atypical multiple mole-melanoma syndrome. *J Med Genet* **15**, 352–6 (1978).
- [365] Mize, D. E., Bishop, M., Resse, E. & Sluzevich, J. Familial atypical multiple mole melanoma syndrome. *Bethesda, MD: National Center for Biotechnology Information* (2009).
- [366] Vasen, H. F. *et al.* Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). *Int J Cancer* **87**, 809–11 (2000).
- [367] Shekar, S. N. *et al.* A population-based study of Australian twins with melanoma suggests a strong genetic contribution to liability. *J Invest Dermatol* **129**, 2211–9 (2009).
- [368] Law, M. H., Macgregor, S. & Hayward, N. K. Melanoma genetics: recent findings take us beyond well-traveled pathways. *J Invest Dermatol* **132**, 1763–74 (2012).
- [369] Coory, M. *et al.* Trends for *in situ* and invasive melanoma in Queensland, Australia, 1982–2002. *Cancer Causes Control* **17**, 21–7 (2006).
- [370] Leachman, S. A. *et al.* Selection criteria for genetic assessment of patients with familial melanoma. *J Am Acad Dermatol* **61**, 677.e1–14 (2009).
- [371] Lesueur, F. *et al.* The contribution of large genomic deletions at the cdkn2a locus to the burden of familial melanoma. *Br J Cancer* **99**, 364–70 (2008).
- [372] Eletr, Z. M. & Wilkinson, K. D. An emerging model for BAP1’s role in regulating cell cycle progression. *Cell Biochem Biophys* **60**, 3–11 (2011).
- [373] Marcand, S., Brevet, V., Mann, C. & Gilson, E. Cell cycle restriction of telomere elongation. *Curr Biol* **10**, 487–90 (2000).

- [374] Teer, J. K. & Mullikin, J. C. Exome sequencing: the sweet spot before whole genomes. *Hum Mol Genet* **19**, R145–51 (2010).
- [375] Singleton, A. B. Exome sequencing: a transformative technology. *Lancet Neurol* **10**, 942–6 (2011).
- [376] Robles-Espinoza, C. D. *et al.* *POT1* loss-of-function variants predispose to familial melanoma. *Nat Genet* **46**, 478–81 (2014).
- [377] Li, H. & Durbin, R. Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* **25**, 1754–60 (2009).
- [378] DePristo, M. A. *et al.* A framework for variation discovery and genotyping using next-generation DNA sequencing data. *Nat Genet* **43**, 491–8 (2011).
- [379] McKenna, A. *et al.* The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. *Genome Res* **20**, 1297–303 (2010).
- [380] Li, H. *et al.* The Sequence Alignment/Map format and SAMtools. *Bioinformatics* **25**, 2078–9 (2009).
- [381] The Single Nucleotide Polymorphism Database (dbSNP). URL <http://www.ncbi.nlm.nih.gov/projects/SNP/>.
- [382] Ledergerber, C. & Dessimoz, C. Base-calling for next-generation sequencing platforms. *Brief Bioinform* **12**, 489–97 (2011).
- [383] Durtschi, J., Margraf, R. L., Coonrod, E. M., Mallempati, K. C. & Voelkerding, K. V. VarBin, a novel method for classifying true and false positive variants in NGS data. *BMC Bioinformatics* **14 Suppl 13**, S2 (2013).
- [384] Li, H. A statistical framework for SNP calling, mutation discovery, association mapping and population genetical parameter estimation from sequencing data. *Bioinformatics* **27**, 2987–93 (2011).
- [385] Danecek, P. *et al.* The variant call format and VCFtools. *Bioinformatics* **27**, 2156–8 (2011).
- [386] McLaren, W. *et al.* Deriving the consequences of genomic variants with the Ensembl API and SNP Effect Predictor. *Bioinformatics* **26**, 2069–70 (2010).

- [387] Rashid, M., Robles-Espinoza, C. D., Rust, A. G. & Adams, D. J. Cake: a bioinformatics pipeline for the integrated analysis of somatic variants in cancer genomes. *Bioinformatics* **29**, 2208–10 (2013).
- [388] Meacham, F. *et al.* Identification and correction of systematic error in high-throughput sequence data. *BMC Bioinformatics* **12**, 451 (2011).
- [389] Ensembl Variation - Predicted data. URL [http://www.ensembl.org/info/genome/variation/predicted\\_data.html](http://www.ensembl.org/info/genome/variation/predicted_data.html).
- [390] The Sequence Ontology project. URL <http://www.sequenceontology.org/>.
- [391] Subramanian, A. *et al.* Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A* **102**, 15545–50 (2005).
- [392] Kanehisa, M. & Goto, S. KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Res* **28**, 27–30 (2000).
- [393] Croft, D. *et al.* Reactome: a database of reactions, pathways and biological processes. *Nucleic Acids Res* **39**, D691–7 (2011).
- [394] BioCarta. URL <http://www.biocarta.com/genes/index.asp>.
- [395] Flicek, P. *et al.* Ensembl 2012. *Nucleic Acids Res* **40**, D84–90 (2012).
- [396] Wang, X., Terfve, C., Rose, J. C. & Markowetz, F. HTSanalyzeR: an R/Bioconductor package for integrated network analysis of high-throughput screens. *Bioinformatics* **27**, 879–80 (2011).
- [397] Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)* 289–300 (1995).
- [398] Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet* **88**, 76–82 (2011).
- [399] Muddyman, D., Smee, C., Griffin, H. & Kaye, J. Implementing a successful data-management framework: the UK10K managed access model. *Genome Med* **5**, 100 (2013).

- [400] Tian, C., Gregersen, P. K. & Seldin, M. F. Accounting for ancestry: population substructure and genome-wide association studies. *Hum Mol Genet* **17**, R143–50 (2008).
- [401] Stein, L. D. Graphic Design (GD) module for Perl. URL <https://github.com/lstein/Perl-GD>.
- [402] Finn, R. D. *et al.* The Pfam protein families database. *Nucleic Acids Res* **38**, D211–22 (2010).
- [403] Ferla, R. *et al.* Founder mutations in *BRCA1* and *BRCA2* genes. *Ann Oncol* **18 Suppl 6**, vi93–8 (2007).
- [404] Liu, Y., Wang, L. & Zheng, P. X-linked tumor suppressors: perplexing inheritance, a unique therapeutic opportunity. *Trends Genet* **26**, 260–5 (2010).
- [405] HUGO Gene Nomenclature Committee: Symbol report: WASH6P. URL [http://www.genenames.org/cgi-bin/gene\\_symbol\\_report?q=data/hgnc\\_data.php&hgnc\\_id=31685](http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=31685).
- [406] Caputo, S. *et al.* Description and analysis of genetic variants in French hereditary breast and ovarian cancer families recorded in the UMD-BRCA1/BRCA2 databases. *Nucleic Acids Res* **40**, D992–1002 (2012).
- [407] Vallée, M. P. *et al.* Classification of missense substitutions in the BRCA genes: a database dedicated to Ex-UVs. *Hum Mutat* **33**, 22–8 (2012).
- [408] Farnolli, M. C. *et al.* Contribution of melanocortin-1 receptor gene variants to sporadic cutaneous melanoma risk in a population in central Italy: a case-control study. *Melanoma Res* **16**, 175–82 (2006).
- [409] Galore-Haskel, G. *et al.* *MC1R* variant alleles and malignant melanoma risk in Israel. *Eur J Cancer* **45**, 2015–22 (2009).
- [410] Landi, M. T. *et al.* *MC1R*, ASIP, and DNA repair in sporadic and familial melanoma in a Mediterranean population. *J Natl Cancer Inst* **97**, 998–1007 (2005).
- [411] Cust, A. E. *et al.* *MC1R* genotypes and risk of melanoma before age 40 years: a population-based case-control-family study. *Int J Cancer* **131**, E269–81 (2012).

- [412] Fernandez, L. *et al.* *MC1R*: three novel variants identified in a malignant melanoma association study in the Spanish population. *Carcinogenesis* **28**, 1659–64 (2007).
- [413] Brumbaugh, K. M. *et al.* The mRNA surveillance protein hSMG-1 functions in genotoxic stress response pathways in mammalian cells. *Mol Cell* **14**, 585–98 (2004).
- [414] Aoude, L. G. *et al.* Nonsense mutations in the shelterin complex genes *ACD* and *TERF2IP* in familial melanoma. *J Natl Cancer Inst* (2014).
- [415] Bataille, V. *et al.* The association between naevi and melanoma in populations with different levels of sun exposure: a joint case-control study of melanoma in the UK and Australia. *Br J Cancer* **77**, 505–10 (1998).
- [416] Aitken, J. F., Green, A. C., MacLennan, R., Youl, P. & Martin, N. G. The Queensland Familial Melanoma Project: study design and characteristics of participants. *Melanoma Res* **6**, 155–65 (1996).
- [417] Ng, P. C. & Henikoff, S. SIFT: Predicting amino acid changes that affect protein function. *Nucleic Acids Res* **31**, 3812–4 (2003).
- [418] Adzhubei, I. A. *et al.* A method and server for predicting damaging missense mutations. *Nat Methods* **7**, 248–9 (2010).
- [419] Wilson, D. *et al.* SUPERFAMILY—sophisticated comparative genomics, data mining, visualization and phylogeny. *Nucleic Acids Res* **37**, D380–6 (2009).
- [420] Pfam. Family: *TPP1* (PF10341) (2014). URL [http://pfam.xfam.org/family/](http://pfam.xfam.org/family/PF10341)  
[PF10341](http://pfam.xfam.org/family/PF10341).
- [421] Zheng, X. *et al.* A high-performance computing toolset for relatedness and principal component analysis of SNP data. *Bioinformatics* **28**, 3326–8 (2012).
- [422] Purcell, S. *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81**, 559–75 (2007).
- [423] de Lange, T. Shelterin: the protein complex that shapes and safeguards human telomeres. *Genes Dev* **19**, 2100–10 (2005).
- [424] Ye, J. Z.-S. *et al.* POT1-interacting protein PIP1: a telomere length regulator that recruits POT1 to the TIN2/TRF1 complex. *Genes Dev* **18**, 1649–54 (2004).

- [425] Robles-Espinoza, C. D., del Castillo Velasco-Herrera, M., Hayward, N. K. & Adams, D. J. Telomere-regulating genes and the telomere interactome in familial cancers. *Mol Cancer Res* (2014).
- [426] Denning, G., Jamieson, L., Maquat, L. E., Thompson, E. A. & Fields, A. P. Cloning of a novel phosphatidylinositol kinase-related kinase: characterization of the human SMG-1 RNA surveillance protein. *J Biol Chem* **276**, 22709–14 (2001).
- [427] McIlwain, D. R. *et al.* Smg1 is required for embryogenesis and regulates diverse genes via alternative splicing coupled to nonsense-mediated mRNA decay. *Proc Natl Acad Sci U S A* **107**, 12186–91 (2010).
- [428] Chang, Y.-F., Imam, J. S. & Wilkinson, M. F. The nonsense-mediated decay RNA surveillance pathway. *Annu Rev Biochem* **76**, 51–74 (2007).
- [429] Yamashita, A., Ohnishi, T., Kashima, I., Taya, Y. & Ohno, S. Human SMG-1, a novel phosphatidylinositol 3-kinase-related protein kinase, associates with components of the mRNA surveillance complex and is involved in the regulation of nonsense-mediated mRNA decay. *Genes Dev* **15**, 2215–28 (2001).
- [430] Chen, R.-Q. *et al.* Kinome siRNA screen identifies SMG-1 as a negative regulator of hypoxia-inducible factor-1alpha in hypoxia. *J Biol Chem* **284**, 16752–8 (2009).
- [431] Oliveira, V. *et al.* A protective role for the human SMG-1 kinase against tumor necrosis factor-alpha-induced apoptosis. *J Biol Chem* **283**, 13174–84 (2008).
- [432] Cho, H., Han, S., Park, O. H. & Kim, Y. K. SMG1 regulates adipogenesis via targeting of staufen1-mediated mRNA decay. *Biochim Biophys Acta* **1829**, 1276–87 (2013).
- [433] Henderson-Smith, A. *et al.* SMG1 identified as a regulator of Parkinson's disease-associated alpha-synuclein through siRNA screening. *PLoS One* **8**, e77711 (2013).
- [434] 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).
- [435] Le, P. N., Maranon, D. G., Altina, N. H., Battaglia, C. L. R. & Bailey, S. M. TERRA, hnRNP A1, and DNA-PKcs Interactions at Human Telomeres. *Front Oncol* **3**, 91 (2013).

- [436] Roberts, T. L. *et al.* Smg1 haploinsufficiency predisposes to tumor formation and inflammation. *Proc Natl Acad Sci U S A* **110**, E285–94 (2013).
- [437] Ding, L. *et al.* Somatic mutations affect key pathways in lung adenocarcinoma. *Nature* **455**, 1069–75 (2008).
- [438] Forbes, S. A. *et al.* COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer. *Nucleic Acids Res* **39**, D945–50 (2011).
- [439] Neben, K. *et al.* Distinct gene expression patterns associated with FLT3- and NRAS-activating mutations in acute myeloid leukemia with normal karyotype. *Oncogene* **24**, 1580–8 (2005).
- [440] Tiedemann, R. E. *et al.* Kinome-wide RNAi studies in human multiple myeloma identify vulnerable kinase targets, including a lymphoid-restricted kinase, GRK6. *Blood* **115**, 1594–604 (2010).
- [441] Mishra, P. J. *et al.* Dissection of RAS downstream pathways in melanomagenesis: a role for Ral in transformation. *Oncogene* **29**, 2449–56 (2010).
- [442] ATCC:A-375 (ATCC® CRL-1619™) (2014). URL <http://www.atcc.org/products/all/CRL-1619.aspx>.
- [443] Blackburn, E. H. & Gall, J. G. A tandemly repeated sequence at the termini of the extrachromosomal ribosomal RNA genes in *Tetrahymena*. *J Mol Biol* **120**, 33–53 (1978).
- [444] O’Sullivan, R. J. & Karlseder, J. Telomeres: protecting chromosomes against genome instability. *Nat Rev Mol Cell Biol* **11**, 171–81 (2010).
- [445] Xin, H. *et al.* TPP1 is a homologue of ciliate TEBP-beta and interacts with POT1 to recruit telomerase. *Nature* **445**, 559–62 (2007).
- [446] Linger, B. R. & Price, C. M. Conservation of telomere protein complexes: shuffling through evolution. *Crit Rev Biochem Mol Biol* **44**, 434–46 (2009).
- [447] Bianchi, A., Smith, S., Chong, L., Elias, P. & de Lange, T. TRF1 is a dimer and bends telomeric DNA. *EMBO J* **16**, 1785–94 (1997).

- [448] Court, R., Chapman, L., Fairall, L. & Rhodes, D. How the human telomeric proteins TRF1 and TRF2 recognize telomeric DNA: a view from high-resolution crystal structures. *EMBO Rep* **6**, 39–45 (2005).
- [449] Loayza, D., Parsons, H., Donigian, J., Hoke, K. & de Lange, T. DNA binding features of human POT1: a nonamer 5'-TAGGGTTAG-3' minimal binding site, sequence specificity, and internal binding to multimeric sites. *J Biol Chem* **279**, 13241–8 (2004).
- [450] Hockemeyer, D. *et al.* Telomere protection by mammalian Pot1 requires interaction with Tpp1. *Nat Struct Mol Biol* **14**, 754–61 (2007).
- [451] Nandakumar, J. & Cech, T. R. Finding the end: recruitment of telomerase to telomeres. *Nat Rev Mol Cell Biol* **14**, 69–82 (2013).
- [452] Ye, J. Z.-S. *et al.* TIN2 binds TRF1 and TRF2 simultaneously and stabilizes the TRF2 complex on telomeres. *J Biol Chem* **279**, 47264–71 (2004).
- [453] Chiang, Y. J., Kim, S.-H., Tessarollo, L., Campisi, J. & Hodes, R. J. Telomere-associated protein TIN2 is essential for early embryonic development through a telomerase-independent pathway. *Mol Cell Biol* **24**, 6631–4 (2004).
- [454] Hockemeyer, D., Daniels, J.-P., Takai, H. & de Lange, T. Recent expansion of the telomeric complex in rodents: Two distinct POT1 proteins protect mouse telomeres. *Cell* **126**, 63–77 (2006).
- [455] Karlseder, J. *et al.* Targeted deletion reveals an essential function for the telomere length regulator Trf1. *Mol Cell Biol* **23**, 6533–41 (2003).
- [456] 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).
- [457] Sfeir, A. & de Lange, T. Removal of shelterin reveals the telomere end-protection problem. *Science* **336**, 593–7 (2012).
- [458] Stansel, R. M., de Lange, T. & Griffith, J. D. T-loop assembly in vitro involves binding of TRF2 near the 3' telomeric overhang. *EMBO J* **20**, 5532–40 (2001).
- [459] Hockemeyer, D., Sfeir, A. J., Shay, J. W., Wright, W. E. & de Lange, T. POT1 protects telomeres from a transient DNA damage response and determines how human chromosomes end. *EMBO J* **24**, 2667–78 (2005).

- [460] Loayza, D. & De Lange, T. POT1 as a terminal transducer of TRF1 telomere length control. *Nature* **423**, 1013–8 (2003).
- [461] Liu, D. *et al.* PTOP interacts with POT1 and regulates its localization to telomeres. *Nat Cell Biol* **6**, 673–80 (2004).
- [462] Ramsay, A. J. *et al.* *POT1* mutations cause telomere dysfunction in chronic lymphocytic leukemia. *Nat Genet* **45**, 526–30 (2013).
- [463] Wang, F. *et al.* The POT1-TPP1 telomere complex is a telomerase processivity factor. *Nature* **445**, 506–10 (2007).
- [464] Colgin, L. M., Baran, K., Baumann, P., Cech, T. R. & Reddel, R. R. Human POT1 facilitates telomere elongation by telomerase. *Curr Biol* **13**, 942–6 (2003).
- [465] Kendellen, M. F., Barrientos, K. S. & Counter, C. M. POT1 association with TRF2 regulates telomere length. *Mol Cell Biol* **29**, 5611–9 (2009).
- [466] Yeo, G. & Burge, C. B. Maximum entropy modeling of short sequence motifs with applications to RNA splicing signals. *J Comput Biol* **11**, 377–94 (2004).
- [467] Sievers, F. *et al.* Fast, scalable generation of high-quality protein multiple sequence alignments using Clustal Omega. *Mol Syst Biol* **7**, 539 (2011).
- [468] Waterhouse, A. M., Procter, J. B., Martin, D. M. A., Clamp, M. & Barton, G. J. Jalview Version 2—a multiple sequence alignment editor and analysis workbench. *Bioinformatics* **25**, 1189–91 (2009).
- [469] Felsenstein, J. PHYLIP-Phylogeny Inference Package (Version 3.2). *Cladistics* **5**, 164–166 (1989).
- [470] Nandakumar, J., Podell, E. R. & Cech, T. R. How telomeric protein POT1 avoids RNA to achieve specificity for single-stranded DNA. *Proc Natl Acad Sci U S A* **107**, 651–6 (2010).
- [471] Lei, M., Podell, E. R. & Cech, T. R. Structure of human POT1 bound to telomeric single-stranded DNA provides a model for chromosome end-protection. *Nat Struct Mol Biol* **11**, 1223–9 (2004).
- [472] PyMOL Molecular Graphics System, Version 0.99. URL <http://www.pymol.org/>.

- [473] Baumann, P., Podell, E. & Cech, T. R. Human Pot1 (protection of telomeres) protein: cytolocalization, gene structure, and alternative splicing. *Mol Cell Biol* **22**, 8079–87 (2002).
- [474] Ding, Z. *et al.* Estimating telomere length from whole genome sequence data. *Nucleic Acids Res* **42**, e75 (2014).
- [475] Harrell, F. E. Hmisc S function library (2004). URL <http://biostat.mc.vanderbilt.edu/s/Hmisc>.
- [476] Silverman, B. *Density estimation for statistics and data analysis* (Chapman and Hall, 1986).
- [477] McGrath, M., Wong, J. Y. 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).
- [478] Cawthon, R. M. Telomere measurement by quantitative PCR. *Nucleic Acids Res* **30**, e47 (2002).
- [479] Pooley, K. A. *et al.* Telomere length in prospective and retrospective cancer case-control studies. *Cancer Res* **70**, 3170–6 (2010).
- [480] Bojesen, S. E. *et al.* Multiple independent variants at the *TERT* locus are associated with telomere length and risks of breast and ovarian cancer. *Nat Genet* **45**, 371–84, 384e1–2 (2013).
- [481] Gonzalez-Perez, A. *et al.* IntOGen-mutations identifies cancer drivers across tumor types. *Nat Methods* **10**, 1081–2 (2013).
- [482] Gonzalez-Perez, A. & Lopez-Bigas, N. Functional impact bias reveals cancer drivers. *Nucleic Acids Res* **40**, e169 (2012).
- [483] Cooper, M. A. Optical biosensors in drug discovery. *Nat Rev Drug Discov* **1**, 515–28 (2002).
- [484] Shi, J. *et al.* Rare missense variants in *POT1* predispose to familial cutaneous malignant melanoma. *Nat Genet* **46**, 482–6 (2014).
- [485] Alter, B. P., Giri, N., Savage, S. A. & Rosenberg, P. S. Cancer in dyskeratosis congenita. *Blood* **113**, 6549–57 (2009).

- [486] Shiloh, Y. Ataxia-telangiectasia and the Nijmegen breakage syndrome: related disorders but genes apart. *Annu Rev Genet* **31**, 635–62 (1997).
- [487] Arora, H. *et al.* Bloom syndrome. *Int J Dermatol* **53**, 798–802 (2014).
- [488] Gramatges, M. M., Telli, M. L., Balise, R. & Ford, J. M. Longer relative telomere length in blood from women with sporadic and familial breast cancer compared with healthy controls. *Cancer Epidemiol Biomarkers Prev* **19**, 605–13 (2010).
- [489] Svenson, U. *et al.* Breast cancer survival is associated with telomere length in peripheral blood cells. *Cancer Res* **68**, 3618–23 (2008).
- [490] Pooley, K. A. *et al.* Lymphocyte telomere length is long in *BRCA1* and *BRCA2* mutation carriers regardless of cancer-affected status. *Cancer Epidemiol Biomarkers Prev* **23**, 1018–24 (2014).
- [491] Lan, Q. *et al.* A prospective study of telomere length measured by monochrome multiplex quantitative PCR and risk of non-Hodgkin lymphoma. *Clin Cancer Res* **15**, 7429–33 (2009).
- [492] Shen, M. *et al.* A prospective study of telomere length measured by monochrome multiplex quantitative PCR and risk of lung cancer. *Lung Cancer* **73**, 133–7 (2011).
- [493] Lan, Q. *et al.* Longer telomere length in peripheral white blood cells is associated with risk of lung cancer and the rs2736100 (*CLPTM1L-TERT*) polymorphism in a prospective cohort study among women in China. *PLoS One* **8**, e59230 (2013).
- [494] Anic, G. M. *et al.* Telomere length and risk of melanoma, squamous cell carcinoma, and basal cell carcinoma. *Cancer Epidemiol* **37**, 434–9 (2013).
- [495] Burke, L. S. *et al.* Telomere length and the risk of cutaneous malignant melanoma in melanoma-prone families with and without *CDKN2A* mutations. *PLoS One* **8**, e71121 (2013).
- [496] Nan, H. *et al.* Shorter telomeres associate with a reduced risk of melanoma development. *Cancer Res* **71**, 6758–63 (2011).
- [497] Kuilman, T., Michaloglou, C., Mooi, W. J. & Peper, D. S. The essence of senescence. *Genes Dev* **24**, 2463–79 (2010).

- [498] Armanios, M. & Blackburn, E. H. The telomere syndromes. *Nat Rev Genet* **13**, 693–704 (2012).
- [499] Yang, Q., Zheng, Y.-L. & Harris, C. C. POT1 and TRF2 cooperate to maintain telomeric integrity. *Mol Cell Biol* **25**, 1070–80 (2005).
- [500] Heidenreich, B. *et al.* Telomerase reverse transcriptase promoter mutations in primary cutaneous melanoma. *Nat Commun* **5**, 3401 (2014).
- [501] Park, J.-I. *et al.* Telomerase modulates Wnt signalling by association with target gene chromatin. *Nature* **460**, 66–72 (2009).
- [502] Maida, Y. *et al.* An RNA-dependent RNA polymerase formed by TERT and the *RMRP* RNA. *Nature* **461**, 230–5 (2009).
- [503] Gilchrest, B. A., Eller, M. S. & Yaar, M. Telomere-mediated effects on melanogenesis and skin aging. *J Investig Dermatol Symp Proc* **14**, 25–31 (2009).
- [504] 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).
- [505] Rochette, P. J. & Brash, D. E. Human telomeres are hypersensitive to UV-induced DNA Damage and refractory to repair. *PLoS Genet* **6**, e1000926 (2010).
- [506] Wang, H. *et al.* One-step generation of mice carrying mutations in multiple genes by CRISPR/Cas-mediated genome engineering. *Cell* **153**, 910–8 (2013).
- [507] Kipling, D. & Cooke, H. J. Hypervariable ultra-long telomeres in mice. *Nature* **347**, 400–2 (1990).
- [508] Blasco, M. A. *et al.* Telomere shortening and tumor formation by mouse cells lacking telomerase RNA. *Cell* **91**, 25–34 (1997).
- [509] Robles-Espinoza, C. D. & Adams, D. J. Cross-species analysis of mouse and human cancer genomes. *Cold Spring Harb Protoc* **2014**, 350–8 (2014).
- [510] Moniz, L. S. & Stambolic, V. Nek10 mediates G2/M cell cycle arrest and MEK autoactivation in response to UV irradiation. *Mol Cell Biol* **31**, 30–42 (2011).
- [511] Dreszer, T. R. *et al.* The UCSC Genome Browser database: extensions and updates 2011. *Nucleic Acids Res* **40**, D918–23 (2012).

