



Review

Cite this article: Ujvari B, Klaassen M, Raven N, Russell T, Vittecoq M, Hamede R, Thomas F, Madsen T. 2018 Genetic diversity, inbreeding and cancer. *Proc. R. Soc. B* **285**: 20172589. <http://dx.doi.org/10.1098/rspb.2017.2589>

Received: 16 November 2017

Accepted: 28 February 2018

Subject Category:

Evolution

Subject Areas:

evolution, genetics, ecology

Keywords:

genetic diversity, inbreeding, oncogenic mutations, oncogenic pathogens, human and wildlife cancer

Author for correspondence:

Thomas Madsen

e-mail: madsen@uow.edu.au

†These authors contributed equally to the work.

Electronic supplementary material is available online at <https://dx.doi.org/10.6084/m9.figshare.c.4024456>.

Genetic diversity, inbreeding and cancer

Beata Ujvari^{1,2,†}, Marcel Klaassen¹, Nynke Raven¹, Tracey Russell³, Marion Vittecoq⁴, Rodrigo Hamede^{1,2}, Frédéric Thomas⁵ and Thomas Madsen^{1,6,†}

¹Centre for Integrative Ecology, School of Life and Environmental Sciences, Deakin University, Waurn Ponds, Victoria 3216, Australia

²School of Biological Sciences, University of Tasmania, Private Bag 55, Hobart, Tasmania 7001, Australia

³School of Life and Environmental Sciences, University of Sydney, Sydney, New South Wales 2006, Australia

⁴Institut de Recherche de la Tour du Valat, le Sambuc, 13200 Arles, France

⁵CREEC/MIVEGEC, UMR IRD/CNRS/UM 5290, 911 Avenue Agropolis, BP 64501, 34394 Montpellier Cedex 5, France

⁶School of Biological Sciences, University of Wollongong, Wollongong, New South Wales 2522, Australia

BU, 0000-0003-2391-2988; TM, 0000-0002-0998-8372

Genetic diversity is essential for adaptive capacities, providing organisms with the potential of successfully responding to intrinsic and extrinsic challenges. Although a clear reciprocal link between genetic diversity and resistance to parasites and pathogens has been established across taxa, the impact of loss of genetic diversity by inbreeding on the emergence and progression of non-communicable diseases, such as cancer, has been overlooked. Here we provide an overview of such associations and show that low genetic diversity and inbreeding associate with an increased risk of cancer in both humans and animals. Cancer being a multifaceted disease, loss of genetic diversity can directly (via accumulation of oncogenic homozygous mutations) and indirectly (via increased susceptibility to oncogenic pathogens) impact abnormal cell emergence and escape of immune surveillance. The observed link between reduced genetic diversity and cancer in wildlife may further imperil the long-term survival of numerous endangered species, highlighting the need to consider the impact of cancer in conservation biology. Finally, the somewhat incongruent data originating from human studies suggest that the association between genetic diversity and cancer development is multifactorial and may be tumour specific. Further studies are therefore crucial in order to elucidate the underpinnings of the interactions between genetic diversity, inbreeding and cancer.

1. Introduction

Genetic diversity provides populations with the ability to respond to challenges, such as parasites/pathogens, predators and environmental perturbations (electronic supplementary material, table S1). Attenuation of genetic diversity has been linked to increased risk of inbreeding depression, resulting in decreased growth rate, fertility, fecundity and offspring viability [1–9], as well as in increased vulnerability to pathogens [10–12]. Loss of genetic diversity therefore has a negative impact on organismal fitness, and limits a population's ability to respond to threats in both the long and short term (for review see [13]). Akin to parasites, malignant transformations that emerge due to environmental challenges, infections and/or host genotype either in isolation or via the interaction between genotype and environment exploit the host for energy and resources, and thereby impair host fitness and pose as a significant selective force [14–16]. Indeed, recent studies have proposed that malignant cells should be regarded as a developing species that behave in a manner akin to parasites [17]. Consequently, multicellular hosts that have the genetic toolkit to recognize and control cancer causing infections and malignant cell proliferation will have a significant fitness advantage over those that lack such mechanisms. Although a clear reciprocal link between genetic diversity and vulnerability to parasites and pathogens has been widely acknowledged

across taxa, so far the vast majority of studies have overlooked how reduced genetic diversity and inbreeding may influence the appearance and progression of non-communicable diseases, such as cancer. Here we discuss how genetic diversity and inbreeding may contribute to increased risk of cancer development and progression in humans and animals.

2. Cancer aetiologies

Cancer, the uncontrolled division of neoplastic cells, is a ubiquitous disease of metazoans [18] and has been proposed to have appeared with one of the major transitions of life (i.e. the transition from unicellularity to multicellularity) [19]. Fossilized bones, mummified tissues and phylogenetic analyses of oncogenic pathogens show that malignant transformations have been afflicting human and animal populations for eons (reviewed in [20]).

Although cancer is a multifactorial disease, only a small proportion of human cancers (less than 10%) originates from inherited mutations [21]. The majority of familial human cancers have been proposed to root from high-penetrance genetic variants or polymorphisms [22]. For example, specific inherited mutations in BRCA1 and BRCA2 genes account for 5–10% of all breast cancers [23], and inherited mutations of the APC gene is associated with 1–2% of all colon cancers [24]. Similarly, cancer predisposition by rare, high-penetrance alleles (e.g. mutations in c-KIT, P53, BRCA1/2) have also been observed in animal malignancies [25–27].

The majority of human cancer cases can be attributed to advanced age [28] and/or to acquired mutations due to environmental factors (including pathogen infections, exposure to pollution or sunlight, as well as lifestyle, economic and behavioural factors) [20,21] (see also <https://www.cancer.gov/about-cancer/causes-prevention/risk>). Human lifestyle particularly is one of the underlying factors of cancer development as almost 25–30% of all cancer-related human deaths are due to tobacco and 30–35% are linked to diet (reviewed in [21]).

Several of the factors resulting in increased cancer prevalence in humans such as smoking, alcohol and diet are highly unlikely to cause cancer in animals (but see [29,30]), whereas stress [31–33], infections (reviewed in [34]) and exposure to environmental carcinogens have been found to increase cancer prevalence in other vertebrates, such as the brown bullhead (*Ameiurus nebulosus*) [35], California sea lion (*Zalophus californianus*) [36] and beluga whales (*Delphinapterus leucas*) [37].

Infections are the direct or indirect underlying factors of a substantial proportion of both human and animal cancers [38]. Pathogens (particularly intracellular parasites) that alter cellular regulatory mechanisms (e.g. apoptosis, cell-cycle arrest), increase cell proliferation rates and break down cellular controls that would prevent oncogenesis can directly contribute to neoplasm formation. Inflammatory responses initiated by pathogen infections may also increase mutation rates and alter proliferation signals, and hence indirectly initiate malignant transformations (reviewed in [38,39]).

Viruses are the major agents of infection-initiated vertebrate cancers, and seven viruses have been now acknowledged as infectious causes of human cancers (e.g. gamma herpes virus indicated in nasopharyngeal, gastric cancers; Hodgkin's lymphoma, Burkitt's lymphoma) [38]. Similarly, many oncogenic viruses have been associated with malignancies in domestic and wild animals, such as

the oncogenic papillomavirus in rabbits [40] and a gamma herpesvirus associated with urogenital carcinoma in California sea lions (*Zalophus californianus*) [41].

Apart from viruses, the most frequent sources of infection-induced cancers are protozoans (e.g. *Plasmodium falciparum*) [42], bacteria (e.g. *Helicobacter pylori*) [43,44] and trematodes (e.g. *Schistosoma haematobium*) [43,45] have all been shown to directly or indirectly cause malignancies. Although rare, contagious cancers without underlying infectious aetiologies do occur in the wild, and eight naturally occurring transmissible cancers—one lineage in dogs [46], two lineages in Tasmanian devils (*Sarcophilus harrisii*) [47,48] and five lineages in bivalves [49]—have so far been recorded.

3. Genetic diversity, inbreeding and cancer in humans

Several reports provide evidence that low genetic diversity and inbreeding may increase cancer risk and that cancer may have a recessive basis in humans [50–52]. For example, thyroid cancer has been found to be associated with significantly higher levels of inbreeding as well as a higher number and longer runs of homozygosity (ROH) [53], and acute leukaemia have been found to be linked to low levels of genetic diversity and inbreeding [54]. Moreover, extended germline homozygosity has been shown to result in an increased risk of lung cancer [55] and homozygosity of the MTHFR gene has been found to be associated with an increased risk of breast cancer [56].

Genome-wide association studies have also found a significant association between recessive alleles/inbreeding and cancer such as Hodgkin's lymphoma [57]. Based on the same methodology, two studies observed that inbreeding and ROH resulted in an increased risk of colorectal cancer [58,59], whereas a third study could not find such an association [60]. Similar dissonant results have been reported from studies focusing on countries with high close-kin unions such as the United Arab Emirates and Qatar, with up to 54% consanguinity prevalence [52,53]. The two studies showed that reduced genetic diversity and inbreeding was associated with a reduced risk of breast, skin, thyroid and female genital cancers, but an increased risk of developing leukaemia, lymphoma, colorectal and prostate cancer [61,62]. The incongruous results observed in some human studies suggest that the effect of genetic diversity and inbreeding on cancer development may be tumour specific.

4. Genetic diversity, inbreeding and cancer in domestic animals

Strong artificial selection and small founder population size during domestication of animals have had the unintentional effect of diminishing genetic diversity, and resulted in the accumulation of deleterious genetic variants. For example, despite their exceptional phenotypic diversity, both domestic dogs and cats have significantly lower genetic diversity compared with their wild conspecifics, and/or their wild ancestors [63–69]. Apart from additional factors, such as anthropogenically induced longer lifespan and altered environment (e.g. diet and exposure to tobacco smoke), the loss of genetic diversity has been linked to the observed

relatively high cancer prevalence in both cats and dogs [70–73]. Data originating from the histopathology analyses of more than 30 000 malignant neoplastic cases of cats and dogs revealed skin being the most frequently affected tissue in both species, and purebred dogs being more prone to develop neoplasms in general [72]. The latter finding has been further supported by a survey from Italy that showed an almost twofold higher incidence rate of malignant tumours in both purebred cats and dogs compared with mixed breeds [73]. These results are not surprising since selective breeding of dogs led to some breeds descending from a few founders with documented increased risk for certain diseases, such as osteosarcoma, histiocytic sarcoma and squamous cell carcinoma [74]. Recent genomic comparison of healthy golden retrievers with golden retrievers suffering from mast cell tumours (MCT) identified potential causative genetic variations in multiple hyaluronidase genes [75], while an other study demonstrated significant association between germline mutations of BRAC1/2 genes and mammary cancer in English springer spaniels [27].

Lymphoma, the most common haematopoietic cancer of cats, can be initiated by retroviral infections—such as feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV)—or by additional factors, such as chronic cigarette smoke exposure and chronic inflammation (reviewed in [76]). In addition, similar to dogs, breed-specific predisposition for lymphoma with a recessive pattern of inheritance has been observed in Siamese cats and Oriental shorthair cats (reviewed in [76]). Selecting phenotypic traits and specific functions may have inadvertently contributed to the increased susceptibility of our feline and canine companions to both infectious and heritable oncogenesis.

5. Genetic diversity, inbreeding and cancer in wildlife

Despite neoplasia being recorded in most metazoans [77], and being common in domesticated animals, it has generally been assumed to be rare in the wild. In our view this is most likely to be due to the fact that cancer prevalence in wildlife is extremely difficult to identify and reports are highly scattered in the scientific literature, and hence challenging to access [18]. In some fish populations cancer prevalence can actually reach 100%, being caused by contagious agents, pollution, inbreeding or the combination of all these factors [18,78]. Moreover, the high cancer prevalence (26%) recorded in some populations of California sea lions (*Zalophus californianus*) has been suggested to be caused by a herpesvirus and/or persistent organic pollutants, but a high prevalence of urogenital carcinoma has been linked to loss of genetic diversity at a single locus, the heparanase 2 gene (HPSE2) [79]. Additionally, two recent studies have observed a link between low genetic diversity and high cancer prevalence (greater than 50%) in Santa Catalina Island foxes (*Urocyon littoralis catalinae*) [80,81] and the South African Cape mountain zebra (*Equus zebra zebra*) [82–84].

6. Genetic diversity, inbreeding and cancer development

Cancer being a multifaceted disease, loss of genetic diversity and inbreeding can impact cancer emergence both directly

and indirectly (electronic supplementary material, table S2). Reduction of population size, cultural traditions promoting consanguineous marriages and natural selection purging favouring certain haplotypes contribute to an increased likelihood of a reduction in genetic diversity, which may result in a higher frequency of long stretches of ROH regions [85,86]. ROH harbour disproportionately more deleterious homozygotes than other parts of the genome [85], and the presence of identical pathogenic variants of both alleles have been shown to result in recessive disorders [51,87]. Reduced genetic diversity magnifies the impact of deleterious homozygous mutations [85], and genomic studies suggest that homozygosity of some germline low-penetrance cancer genes act as significant contributing factors to the development of human oesophageal [88], oral [89], lung [90,91], bladder [92], acute lymphocytic leukaemia [93] and breast cancers [61,94,95].

Apart from the direct role of cancer increasing homozygous genomic regions, a general reduction in genetic diversity can also contribute to the development of tumours via infectious agents such as viruses (e.g. [34,38,96]). Loss of genetic diversity at important immune gene loci such as the major histocompatibility complex (MHC), Toll-like receptors (TLRs) and type I and II interferons [12,97], can increase the risk of pathogen infections that either directly or indirectly initiate malignant transformations. For example, genetic variants of interferon genes have not only been associated with pathogen resistance (including carcinogenic helminth infections) [98–102], but have also been shown to influence melanoma progression and survival in humans [103]. Furthermore, hepatitis C virus (HCV), one of the most common chronic blood-borne infections, results in chronic hepatitis in approximately 80% of infected patients, and leads to death in up to 5% of these patients from hepatocellular carcinoma (HCC) or liver cancer [104]. A complex interplay between host genetics, immunology and viral factors has been proposed to determine the outcome of HCV infection [104–107]. Ethnic background, immune gene polymorphism as well as the presence of specific alleles (e.g. interleukin 28B, inhibitory natural killer cell receptors and MHC classes I and II, and variants of interferon (IFN)L3-IFNL4, etc.) have been identified as key elements of HCV clearance, and consequent disease progression [104–107].

Helicobacter pylori infections, an underlying factor of gastric cancer, provide an excellent example of how the host genotype may indirectly contribute to initiation of malignant transformations. *Helicobacter pylori* affects at least 50% of humans worldwide, and hence owns the uncoveted title of being ‘the most common single chronic bacterial infection in the world’ [108]. The bacteria and their human host have a long evolutionary history; anatomically modern humans were already infected by *H. pylori* prior to leaving Africa and the close association remains ever since [109]. The majority of infected individuals develop no significant disease, but clinical outcomes range from asymptomatic gastritis to peptic ulcer disease and gastric cancer [108]. Risk of infection, prevalence and disease outcomes have been linked to ethnicity, socioeconomic status, and behavioural and genetic variables [110]. One of the most challenging scientific conundrums is to explain individual predisposition to the disease—why some individuals develop serious sequelae of *H. pylori* infections, while others don’t [108].

Considerable focus has been placed on understanding bacterial and host genetic factors, and a twin study showed that both host genetic and environmental factors ('rearing environment') influence the acquisition of *H. pylori* infection [111]. Importantly, host proinflammatory genetic makeup appears to have a major contribution to the pathogenesis of gastric cancer. Individuals with proinflammatory genotypes (IL-1B-511*T carriers/IL-1RN*2 homozygotes) have an increased risk for gastric carcinoma. The carriers of the specific genotypes generate heightened inflammatory response to *H. pylori* infection, which ultimately creates a chronically inflamed environment with elevated oxidative/genotoxic stress (due to hypochlorhydria) and eventually initiates a proneoplastic drive [108,112]. Apart from the genetic factors, socioeconomic variables and industrialized environments have also been associated with chronic gastritis, peptic ulcer disease and gastric cancers [110]. While gastric carcinoma is more common in the developing world, the less severe chronic gastritis and peptic ulcers are more frequently reported from the developed world [110]. These might be due to reporting, or due to disease presentation being related to the age of infection (i.e. early childhood infections are postulated to develop over time into pre-malignant changes and eventually gastric carcinoma, in contrast to infection during adulthood, which is more likely to result in ulcer disease [110]). Regional and ethnic variations of *H. pylori* aetiology have been observed and discussed since the links between infection, peptic ulcer disease and gastric adenocarcinomas [113] have been established (reviewed in [114]). More recent studies identify environmental factors such as food preservation and diet as primary determinants of disease outcomes [114]. *Helicobacter pylori* infection is clearly a complex disease with a long coevolutionary history between the host and its parasite, which requires further studies to determine prevention and treatment strategies [115].

Reduced genetic diversity may also increase susceptibility of endangered wildlife species to pathogens and their associated cancers both in captive populations as well as in the wild. For example, the low genetic diversity of the Australian western barred bandicoots (*Perameles bougainville*) (WBB) [116] has been proposed to be one of the potential underlying factors of high prevalence of papillomatosis and carcinomatosis syndrome (up to 61.4% prevalence in captive breeding facilities) [117]. By using microsatellite markers, Smith & Hughes [116] estimated the WBB's genetic diversity to be one of the lowest ever recorded in marsupials, and Woolford *et al.* [117] proposed that the reduced genetic diversity may contribute to the species's susceptibility to (oncogenic) viruses.

Low genetic diversity at microsatellite loci and lack of variations in mitochondrial DNA (mtDNA) indicate that another endangered species, the snow leopard (*Uncia uncia*), has undergone a genetic bottleneck approximately 8000 years ago [118]. Although no information on cancer prevalence is available from wild snow leopards, a survey by Joslin *et al.* [119] revealed that 9% of mortalities in 66 institutions involved with the Snow Leopard Species Survival Plan (SSP) was due to squamous cell carcinomas (SCC). Papillomas with viral aetiology have been identified as precursors to SCC in felines, including cats and snow leopards [119]. Low genetic diversity of snow leopards may therefore potentially be a contributing factor to viral infections and

ultimately the development of SCCs observed in captivity [119]. Comparative genetics of sarcoid tumour-affected and non-affected mountain zebra (*Equus zebra*) populations revealed that tumour-affected populations had higher homozygosity and relatedness, and lower gene diversity and polymorphism, at 16 microsatellite loci compared with healthy populations (although the levels were not significant ($p = 0.05$) [83]). A study of 371 stranded California sea lions (*Zalophus californianus*) also found a clear association between carcinoma incidence and close genetic relatedness when analysing 11 microsatellite markers [120]. Furthermore, as discussed above, inbreeding depression (estimated based on microsatellite multilocus heterozygosity) and homozygosity of the heparanase 2 gene (HPSE2) locus have been identified as predictors of urogenital carcinoma in sea lions [121]. Finally, the high cancer prevalence observed in the highly inbred Santa Catalina Island foxes [80,81] also strongly suggest an association between loss of genetic diversity and cancer development in wildlife (electronic supplementary material, table S2).

7. Conclusion

As mentioned above, maintenance of genetic diversity is fundamental for adaptive capacities and provides organisms with an ability to successfully respond to challenges caused by parasites/pathogens [122], habitat fragmentation [3,123] and global climate change [124,125]. In contrast to parasites and pathogens cancer, has so far been largely overlooked as a significant determinant of wildlife fitness. The present review, however, suggests that low genetic diversity and inbreeding may elevate cancer development in wildlife, further imperilling the long-term survival of the numerous species presently suffering from low genetic diversity. Our review hence demonstrates the need to consider the effects of cancer in conservation biology.

The results originating from human studies indicate that the effects of genetic diversity and inbreeding on the development of a complex disease such as cancer may be tumour specific. Importantly, by reducing immune function, and thereby increasing the vulnerability to cancer causing parasite/pathogen infections, overall loss of genetic diversity and inbreeding may therefore constitute a significant underpinning of cancer development in humans as well as in other organisms [126,127]. Finally, the link between low genetic diversity/inbreeding and cancer may be just as arduous as the disease itself, and further studies, including genome-wide association studies on both domestic and wild animals, population genetic and genomic analyses of species affected by high prevalence of cancer, and epidemiological studies likening infectious diseases to cancer prevalence, are therefore urgently needed to decipher the underpinnings of such associations.

Ethics. As the manuscript is a review of published work, the study did not require any ethics approval.

Data accessibility. The manuscript is a review of published work and the data used can therefore be accessed from the referred publications.

Authors' contributions. All authors participated in writing both the first and revised versions of the manuscript.

Competing interests. The authors have no competing interests.

Funding. This work was supported by two Eric Guiler Tasmanian devil Research Grants through the Save the Tasmanian Devil appeal of the

University of Tasmania Foundation, by the ANR (Blanc project EVOCAN) by the CNRS (INEE), by an International Associated Laboratory Project France/Australia, by an Australian Academy of Science, FASIC Early Career Fellowship to B.U. and by Deakin University's CRGS Grant. We are also grateful to Mr André Hoffmann,

MAVA foundation, Tour du Valat, for his continuous support of our research.

Acknowledgements. We thank Prof. James DeGregori and one anonymous reviewer for their valuable comments on our manuscript.

References

- Keller LF, Waller DM. 2002 Inbreeding effects in wild populations. *Trends Ecol. Evol.* **17**, 230–241. (doi:10.1016/S0169-5347(02)02489-8)
- Crnokrak P, Roff DA. 1999 Inbreeding depression in the wild. *Heredity* **83**, 260–270. (doi:10.1038/sj.hdy.6885530)
- Madsen T, Shine R, Olsson M, Wittzell H. 1999 Conservation biology: restoration of an inbred adder population. *Nature* **402**, 34–35. (doi:10.1038/46941)
- Madsen T, Stille B, Shine R. 1996 Inbreeding depression in an isolated population of adders *Vipera berus*. *Biol. Conserv.* **75**, 113–118. (doi:10.1016/0006-3207(95)00067-4)
- Madsen T, Ujvari B, Olsson M. 2004 Novel genes continue to enhance population growth in adders (*Vipera berus*). *Biol. Conserv.* **120**, 145–147. (doi:10.1016/j.biocon.2004.01.022)
- Saccheri I, Kuussaari M, Kankare M, Vikman P, Fortelius W, Hanski I. 1998 Inbreeding and extinction in a butterfly metapopulation. *Nature* **392**, 491–494. (doi:10.1038/33136)
- Slate J, Kruuk LE, Marshall TC, Pemberton JM, Clutton-Brock TH. 2000 Inbreeding depression influences lifetime breeding success in a wild population of red deer (*Cervus elaphus*). *Proc. R. Soc. Lond. B* **267**, 1657–1662. (doi:10.1098/rspb.2000.1192)
- Huisman J, Kruuk LEB, Ellis PA, Clutton-Brock T, Pemberton JM. 2016 Inbreeding depression across the lifespan in a wild mammal population. *Proc. Natl Acad. Sci. USA* **113**, 3585–3590. (doi:10.1073/pnas.1518046113)
- Westemeier RL, Brawn JD, Simpson SA, Esker TL, Jansen RW, Walk JW, Kershner EL, Bouzat JL, Paige KN. 1998 Tracking the long-term decline and recovery of an isolated population. *Science* **282**, 1695–1698. (doi:10.1126/science.282.5394.1695)
- O'Brien SJ, Evermann JF. 1988 Interactive influence of infectious disease and genetic diversity in natural populations. *Trends Ecol. Evol.* **3**, 254–259. (doi:10.1016/0169-5347(88)90058-4)
- Townsend AK, Clark AB, McGowan KJ, Miller AD, Buckles EL. 2010 Condition, innate immunity and disease mortality of inbred crows. *Proc. R. Soc. B* **277**, 2875–2883. (doi:10.1098/rspb.2010.0480)
- Ujvari B, Belov K. 2011 Major histocompatibility complex (MHC) markers in conservation biology. *Int. J. Mol. Sci.* **12**, 5168–5186. (doi:10.3390/ijms12085168)
- Altizer S, Harvell D, Friedle E. 2003 Rapid evolutionary dynamics and disease threats to biodiversity. *Trends Ecol. Evol.* **18**, 589–596. (doi:10.1016/j.tree.2003.08.013)
- Ujvari B *et al.* 2016 Cancer and life-history traits: lessons from host-parasite interactions. *Parasitology* **143**, 533–541. (doi:10.1017/s0031182016000147)
- Vittecoq M *et al.* 2013 Cancer: a missing link in ecosystem functioning? *Trends Ecol. Evol.* **28**, 628–635. (doi:10.1016/j.tree.2013.07.005)
- Thomas F *et al.* 2017 The importance of cancer cell communities for animal evolutionary ecology. *Nat. Ecol. Evol.* **1**, 1592–1595. (doi:10.1038/s41559-017-0343-z)
- Duesberg P, Mandrioli D, McCormack A, Nicholson JM. 2011 Is carcinogenesis a form of speciation? *Cell Cycle* **10**, 2100–2114. (doi:10.4161/cc.10.13.16352)
- Madsen T *et al.* 2017 Cancer prevalence and etiology in wild and captive animals. In *Ecology and evolution of cancer* (eds B Ujvari, B Roche, F Thomas), pp. 11–46. New York, NY: Academic Press.
- Szathmari E, Smith JM. 1995 The major evolutionary transitions. *Nature* **374**, 227–232. (doi:10.1038/374227a0)
- Ewald PW. In press. Ancient cancers and infection-induced oncogenesis. *Int. J. Paleopathol.* (doi:10.1016/j.ijpp.2017.08.007)
- Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB. 2008 Cancer is a preventable disease that requires major lifestyle changes. *Pharm. Res.* **25**, 2097–2116. (doi:10.1007/s11095-008-9661-9)
- Balmain A, Gray J, Ponder B. 2003 The genetics and genomics of cancer. *Nat. Genet.* **33**(Suppl), 238–244. (doi:10.1038/ng1107)
- Campeau PM, Foulkes WD, Tischkowitz MD. 2008 Hereditary breast cancer: new genetic developments, new therapeutic avenues. *Hum. Genet.* **124**, 31–42. (doi:10.1007/s00439-008-0529-1)
- Al-Sukhni W, Aronson M, Gallinger S. 2008 Hereditary colorectal cancer syndromes: familial adenomatous polyposis and lynch syndrome. *Surg. Clin. North Am.* **88**, 819–844. (doi:10.1016/j.suc.2008.04.012)
- Gregory-Bryson E, Bartlett E, Kiupel M, Hayes S, Yuzbasiyan-Gurkan V. 2010 Canine and human gastrointestinal stromal tumors display similar mutations in c-KIT exon 11. *BMC Cancer* **10**, 559. (doi:10.1186/1471-2407-10-559)
- Chu LL, Rutteman GR, Kong JM, Ghahremani M, Schmeing M, Misdorp W, van Garderen E, Pelletier J. 1998 Genomic organization of the canine p53 gene and its mutational status in canine mammary neoplasia. *Breast Cancer Res. Treat.* **50**, 11–25. (doi:10.1023/a:1006010526813)
- Rivera P, Melin M, Biagi T, Fall T, Häggström J, Lindblad-Toh K, von Euler H. 2009 Mammary tumor development in dogs is associated with BRCA1 and BRCA2. *Cancer Res.* **69**, 8770. (doi:10.1158/0008-5472.CAN-09-1725)
- DeGregori J. 2012 Challenging the axiom: does the occurrence of oncogenic mutations truly limit cancer development with age? *Oncogene* **32**, 1869. (doi:10.1038/onc.2012.281)
- Reif JS, Cohen D. 1971 The environmental distribution of canine respiratory tract neoplasms. *Arch. Environ. Health* **22**, 136–140. (doi:10.1080/00039896.1971.10665823)
- Reif JS, Dunn K, Ogilvie GK, Harris CK. 1992 Passive smoking and canine lung cancer risk. *Am. J. Epidemiol.* **135**, 234–239. (doi:10.1093/oxfordjournals.aje.a116276)
- Thaker PH *et al.* 2006 Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat. Med.* **12**, 939–944. (doi:10.1038/nm1447)
- Le CP *et al.* 2016 Chronic stress in mice remodels lymph vasculature to promote tumour cell dissemination. *Nat. Commun.* **7**, 10634. (doi:10.1038/ncomms10634)
- Cannas S, Berteselli GV, Piotti P, Talamonti Z, Scaglia E, Stefanello D, Minerio M, Palestini C. 2016 Stress and cancer in dogs: comparison between a population of dogs diagnosed with cancer and a control population—a pilot study. *Maced. Vet. Rev.* **39**, 201–208. (doi:10.1515/macvetrev-2016-0088)
- de Martel C, Franceschi S. 2009 Infections and cancer: established associations and new hypotheses. *Crit. Rev. Oncol. Hematol.* **70**, 183–194. (doi:10.1016/j.critrevonc.2008.07.021)
- Baumann PC, LeBlanc DR, Blazer V, Meier JR, Hurley ST, Kiryu Y. 2008 Prevalence of tumors in brown bullhead from three lakes in Southeastern Massachusetts, 2002. Washington, DC: US Geological Survey Scientific Investigations. See <http://pubs.usgs.gov/sir/2008/5198>.
- Gulland FMD, Trupkiewicz JG, Spraker TR, Lowenstine LJ. 1996 Metastatic carcinoma of probable transitional cell origin in 66 free-living California sea lions (*Zalophus californianus*), 1979 to 1994. *J. Wildl. Dis.* **32**, 250–258. (doi:10.7589/0090-3558-32.2.250)
- Martineau D, Lemberger K, Dallaire A, Labelle P, Lipscomb TP, Michel P, Mikaelian I. 2002 Cancer in wildlife, a case study: beluga from the St. Lawrence estuary, Québec, Canada. *Environ. Health Perspect.* **110**, 285–292. (doi:10.1289/ehp.02110285)

38. Ewald PW, Swain Ewald HA. 2015 Infection and cancer in multicellular organisms. *Phil. Trans. R. Soc. B* **370**, 20140224. (doi:10.1098/rstb.2014.0224)
39. Ewald PW, Swain Ewald HA. 2012 Infection, mutation, and cancer evolution. *J. Mol. Med.* **90**, 535–541. (doi:10.1007/s00109-012-0891-2)
40. Shope RE, Hurst EW. 1933 Infectious papillomatosis or rabbits: with note on the histopathology. *J. Exp. Med.* **58**, 607–624. (doi:10.1084/jem.58.5.607)
41. King DP, Hure MC, Goldstein T, Aldridge BM, Gulland FMD, Saliki JT, Buckles EL, Lowenstine LJ, Stott JL. 2002 Otarine herpesvirus-1: a novel gammaherpesvirus associated with urogenital carcinoma in California sea lions (*Zalophus californianus*). *Vet. Microbiol.* **86**, 131–137. (doi:10.1016/S0378-1135(01)00497-7)
42. Molyneux EM, Rochford R, Griffin B, Newton R, Jackson G, Menon G, Harrison CJ, Israels T, Bailey S. 2012 Burkitt's lymphoma. *Lancet* **379**, 1234–1244. (doi:10.1016/s0140-6736(11)61177-x)
43. Ewald PW, Swain Ewald HA. 2014 Joint infectious causation of human cancers. *Adv. Parasitol.* **84**, 1–26. (doi:10.1016/b978-0-12-800099-1.00001-6)
44. Mager DL. 2006 Bacteria and cancer: cause, coincidence or cure? A review. *J. Transl. Med.* **4**, 14. (doi:10.1186/1479-5876-4-14)
45. Mostafa MH, Sheweita SA, O'Connor PJ. 1999 Relationship between schistosomiasis and bladder cancer. *Clin. Microbiol. Rev.* **12**, 97–111.
46. Murgia C, Pritchard JK, Kim SY, Fassati A, Weiss RA. 2006 Clonal origin and evolution of a transmissible cancer. *Cell* **126**, 477–487. (doi:10.1016/j.cell.2006.05.051)
47. Pearse AM, Swift K. 2006 Allograft theory: transmission of devil facial-tumour disease. *Nature* **439**, 549. (doi:10.1038/439549a)
48. Pye RJ *et al.* 2016 A second transmissible cancer in Tasmanian devils. *Proc. Natl Acad. Sci. USA* **113**, 374–379. (doi:10.1073/pnas.1519691113)
49. Metzger MJ, Villalba A, Carballal MJ, Iglesias D, Sherry J, Reinisch C, Muttray AF, Baldwin SA, Goff SP. 2016 Widespread transmission of independent cancer lineages within multiple bivalve species. *Nature* **534**, 705–709. (doi:10.1038/nature18599)
50. Rudan I *et al.* 2003 Inbreeding and risk of late onset complex disease. *J. Med. Genet.* **40**, 925–932. (doi:10.1136/jmg.40.12.925)
51. Assié G, LaFramboise T, Platzer P, Eng C. 2008 Frequency of germline genomic homozygosity associated with cancer cases. *JAMA* **299**, 1437–1445. (doi:10.1001/jama.299.12.1437)
52. Lebel RR, Gallagher WB. 1989 Wisconsin consanguinity studies. II. Familial adenocarcinomatosis. *Am. J. Med. Genet.* **33**, 1–6. (doi:10.1002/ajmg.1320330102)
53. Thomsen H *et al.* 2016 Runs of homozygosity and inbreeding in thyroid cancer. *BMC Cancer* **16**, 227. (doi:10.1186/s12885-016-2264-7)
54. Feldman JG, Lee SL, Seligman B. 1976 Occurrence of acute leukemia in females in a genetically isolated population. *Cancer* **38**, 2548–2550. (doi:10.1002/1097-0142(197612)38:6<2548::AID-CNCR2820380644>3.0.CO;2-Y)
55. Orloff MS, Zhang L, Bebek G, Eng C. 2012 Integrative genomic analysis reveals extended germline homozygosity with lung cancer risk in the PLCO cohort. *PLoS ONE* **7**, e31975. (doi:10.1371/journal.pone.0031975)
56. Deligezer U, Akisik EE, Dalay N. 2005 Homozygosity at the C677T of the MTHFR gene is associated with increased breast cancer risk in the Turkish population. *In vivo* **19**, 889–893.
57. Thomsen H *et al.* 2016 Evidence of inbreeding in Hodgkin lymphoma. *PLoS ONE* **11**, e0154259. (doi:10.1371/journal.pone.0154259)
58. Bacolod MD, Schemmann GS, Giardina SF, Paty P, Notterman DA, Barany F. 2009 Emerging paradigms in cancer genetics: some important findings from high-density single nucleotide polymorphism array studies. *Cancer Res.* **69**, 723. (doi:10.1158/0008-5472.CAN-08-3543)
59. Bacolod MD *et al.* 2008 The signatures of autozygosity among patients with colorectal cancer. *Cancer Res.* **68**, 2610. (doi:10.1158/0008-5472.CAN-07-5250)
60. Spain SL, Cazier JB, Houlston R, Carvajal-Carmona L, Tomlinson I. 2009 Colorectal cancer risk is not associated with increased levels of homozygosity in a population from the United Kingdom. *Cancer Res.* **69**, 7422–7429. (doi:10.1158/0008-5472.can-09-0659)
61. Denic S, Frampton C, Nicholls MG. 2007 Risk of cancer in an inbred population. *Cancer Detect. Prev.* **31**, 263–269. (doi:10.1016/j.cdp.2007.07.006)
62. Bener A, El Ayoubi HR, Chouchane L, Ali AI, Al-Kubaisi A, Al-Sulaiti H, Teebi AS. 2009 Impact of consanguinity on cancer in a highly endogamous population. *Asian Pac. J. Cancer Prev.* **10**, 35–40.
63. Boyko AR. 2011 The domestic dog: man's best friend in the genomic era. *Genome Biol.* **12**, 216. (doi:10.1186/gb-2011-12-2-216)
64. Freedman AH *et al.* 2014 Genome sequencing highlights the dynamic early history of dogs. *PLoS Genet.* **10**, e1004016. (doi:10.1371/journal.pgen.1004016)
65. Hu Y, Hu S, Wang W, Wu X, Marshall FB, Chen X, Hou L, Wang C. 2014 Earliest evidence for commensal processes of cat domestication. *Proc. Natl Acad. Sci. USA* **111**, 116–120. (doi:10.1073/pnas.1311439110)
66. Lindblad-Toh K *et al.* 2005 Genome sequence, comparative analysis and haplotype structure of the domestic dog. *Nature* **438**, 803–819. (doi:10.1038/nature04338)
67. Marsden CD *et al.* 2016 Bottlenecks and selective sweeps during domestication have increased deleterious genetic variation in dogs. *Proc. Natl Acad. Sci. USA* **113**, 152–157. (doi:10.1073/pnas.1512501113)
68. Montague MJ *et al.* 2014 Comparative analysis of the domestic cat genome reveals genetic signatures underlying feline biology and domestication. *Proc. Natl Acad. Sci. USA* **111**, 17 230–17 235. (doi:10.1073/pnas.1410083111)
69. Vonholdt BM *et al.* 2010 Genome-wide SNP and haplotype analyses reveal a rich history underlying dog domestication. *Nature* **464**, 898–902. (doi:10.1038/nature08837)
70. Dorn CR, Schneider R. 1976 Inbreeding and canine mammary cancer: a retrospective study. *J. Natl Cancer Inst.* **57**, 545–548. (doi:10.1093/jnci/57.3.545)
71. Dorn CR, Taylor DO, Frye FL, Hibbard HH. 1968 Survey of animal neoplasm in Alameda and Contra Costa counties, California. I. Methodology and description of cases. *J. Natl Cancer Inst.* **40**, 295–305.
72. Dorn CR, Taylor DO, Schneider R, Hibbard HH, Klauber MR. 1968 Survey of animal neoplasms in Alameda and Contra Costa Counties, California. II. Cancer morbidity in dogs and cats from Alameda County. *J. Natl Cancer Inst.* **40**, 307–318.
73. Vascellari M, Baioni E, Ru G, Carminato A, Mutinelli F. 2009 Animal tumour registry of two provinces in northern Italy: incidence of spontaneous tumours in dogs and cats. *BMC Vet. Res.* **5**, 39. (doi:10.1186/1746-6148-5-39)
74. Mellers CS, Ostrander EA. 1997 The canine genome. In *Advances in veterinary medicine* (eds. WJ Dodds, JE Womack), pp. 191–216. New York, NY: Academic Press.
75. Arendt ML *et al.* 2015 Genome-wide association study of golden retrievers identifies germ-line risk factors predisposing to mast cell tumours. *PLoS Genet.* **11**, e1005647. (doi:10.1371/journal.pgen.1005647)
76. Louwerens M, London CA, Pedersen NC, Lyons LA. 2005 Feline lymphoma in the post-feline leukemia virus era. *J. Vet. Intern. Med.* **19**, 329–335. (doi:10.1111/j.1939-1676.2005.tb02703.x)
77. Leroi AM, Koufopanou V, Burt A. 2003 Cancer selection. *Nat. Rev. Cancer* **3**, 226–231. (doi:10.1038/nrc1016)
78. Coffee LL, Casey JW, Bowser PR. 2013 Pathology of tumors in fish associated with retroviruses. *Vet. Pathol.* **50**, 390–403. (doi:10.1177/0300985813480529)
79. Browning HM, Gulland FM, Hammond JA, Colegrove KM, Hall AJ. 2015 Common cancer in a wild animal: the California sea lion (*Zalophus californianus*) as an emerging model for carcinogenesis. *Phil. Trans. R. Soc. B* **370**, 20140228. (doi:10.1098/rstb.2014.0228)
80. Funk WC *et al.* 2016 Adaptive divergence despite strong genetic drift: genomic analysis of the evolutionary mechanisms causing genetic differentiation in the island fox (*Urocyon littoralis*). *Mol. Ecol.* **25**, 2176–2194. (doi:10.1111/mec.13605)
81. Vickers TW, Clifford DL, Garcelon DK, King JL, Duncan CL, Gaffney PM, Boyce WM. 2015 Pathology and epidemiology of ceruminous gland tumors among endangered Santa Catalina Island foxes (*Urocyon littoralis catalinae*) in the Channel Islands, USA. *PLoS ONE* **10**, e0143211. (doi:10.1371/journal.pone.0143211)
82. Marais HJ, Page PC. 2011 Treatment of equine sarcoid in seven Cape Mountain zebra (*Equus zebra*

- zebra). *J. Wildl. Dis.* **47**, 917–924. (doi:10.7589/0090-3558-47.4.917)
83. Sasidharan SP, Ludwig A, Harper C, Moodley Y, Bertschinger HJ, Guthrie AJ. 2011 Comparative genetics of sarcoid tumour-affected and non-affected mountain zebra (*Equus zebra*) populations. *South Afr. J. Wildl. Res.* **41**, 36–49. (doi:10.3957/056.041.0117)
 84. Marais HJ, Nel P, Bertschinger HJ, Schoeman JP, Zimmerman D. 2007 Prevalence and body distribution of sarcoids in South African Cape mountain zebra (*Equus zebra zebra*). *J. S Afr. Vet. Assoc.* **78**, 145–148. (doi:10.4102/jsava.v78i3.306)
 85. Szpiech ZA, Xu J, Pemberton TJ, Peng W, Zollner S, Rosenberg NA, Li JZ. 2013 Long runs of homozygosity are enriched for deleterious variation. *Am. J. Hum. Genet.* **93**, 90–102. (doi:10.1016/j.ajhg.2013.05.003)
 86. Shen H, Jin G. 2013 Human genome epidemiology, progress and future. *J. Biomed. Res.* **27**, 167–169. (doi:10.7555/JBR.27.20130040)
 87. Hosking FJ *et al.* 2010 Genome-wide homozygosity signatures and childhood acute lymphoblastic leukemia risk. *Blood* **115**, 4472. (doi:10.1182/blood-2009-09-244483)
 88. Gao CM *et al.* 2002 Glutathione-S-transferases M1 (GSTM1) and GSTT1 genotype, smoking, consumption of alcohol and tea and risk of esophageal and stomach cancers: a case-control study of a high-incidence area in Jiangsu Province, China. *Cancer Lett.* **188**, 95–102. (doi:10.1016/S0304-3835(02)00115-5)
 89. Buch SC, Notani PN, Bhisey RA. 2002 Polymorphism at GSTM1, GSTM3 and GSTT1 gene loci and susceptibility to oral cancer in an Indian population. *Carcinogenesis* **23**, 803–807. (doi:10.1093/carcin/23.5.803)
 90. Benhamou S *et al.* 2002 Meta- and pooled analyses of the effects of glutathione S-transferase M1 polymorphisms and smoking on lung cancer risk. *Carcinogenesis* **23**, 1343–1350. (doi:10.1093/carcin/23.8.1343)
 91. Cascorbi I, Brockmoller J, Mrozikiewicz PM, Bauer S, Loddenkemper R, Roots I. 1996 Homozygous rapid arylamine N-acetyltransferase (NAT2) genotype as a susceptibility factor for lung cancer. *Cancer Res.* **56**, 3961–3966.
 92. Engel LS *et al.* 2002 Pooled analysis and meta-analysis of glutathione S-transferase M1 and bladder cancer: a HuGE review. *Am. J. Epidemiol.* **156**, 95–109. (doi:10.1093/aje/kwf018)
 93. Gutierrez-Camino A, Martin-Guerrero I, Garcia-Orad A. 2017 Genetic susceptibility in childhood acute lymphoblastic leukemia. *Med. Oncol.* **34**, 179. (doi:10.1007/s12032-017-1038-7)
 94. Weber BL, Nathanson KL. 2000 Low penetrance genes associated with increased risk for breast cancer. *Eur. J. Cancer* **36**, 1193–1199. (doi:10.1016/S0959-8049(00)00082-4)
 95. Ambrosone CB, Moysich KB, Furberg H, Freudenheim JL, Bowman ED, Ahmed S, Graham S, Vena JE, Shields PG. 2003 CYP17 genetic polymorphism, breast cancer, and breast cancer risk factors. *Breast Cancer Res. Treat.* **5**, R45–R51. (doi:10.1186/bcr570)
 96. Ewald PW, Swain Ewald HA. 2013 Toward a general evolutionary theory of oncogenesis. *Evol. Appl.* **6**, 70–81. (doi:10.1111/eva.12023)
 97. Acevedo-Whitehouse K, Cunningham AA. 2006 Is MHC enough for understanding wildlife immunogenetics? *Trends Ecol. Evol.* **21**, 433–438. (doi:10.1016/j.tree.2006.05.010)
 98. Coltman DW, Wilson K, Pilkington JG, Stear MJ, Pemberton JM. 2001 A microsatellite polymorphism in the gamma interferon gene is associated with resistance to gastrointestinal nematodes in a naturally-parasitized population of Soay sheep. *Parasitology* **122**, 571–582. (doi:10.1017/S0031182001007570)
 99. Crawford AM *et al.* 2006 Discovery of quantitative trait loci for resistance to parasitic nematode infection in sheep. I. Analysis of outcross pedigrees. *BMC Genomics* **7**, 178. (doi:10.1186/1471-2164-7-178)
 100. Vennervald BJ, Polman K. 2009 Helminths and malignancy. *Parasite Immunol.* **31**, 686–696. (doi:10.1111/j.1365-3024.2009.01163.x)
 101. Ottenhoff THM, Verreck FAW, Hoeve MA, Vosse Evd. 2005 Control of human host immunity to mycobacteria. *Tuberculosis* **85**, 53–64. (doi:10.1016/j.tube.2004.09.011)
 102. Lopez-Maderuelo D, Arnalich F, Serantes R, Gonzalez A, Codoceo R, Madero R, Vazquez JJ, Montiel C. 2003 Interferon-gamma and interleukin-10 gene polymorphisms in pulmonary tuberculosis. *Am. J. Respir. Crit. Care Med.* **167**, 970–975. (doi:10.1164/rccm.200205-438BC)
 103. Lenci RE *et al.* 2012 Influence of genetic variants in type I interferon genes on melanoma survival and therapy. *PLoS ONE* **7**, e50692. (doi:10.1371/journal.pone.0050692)
 104. Campo DS *et al.* 2016 Increased mitochondrial genetic diversity in persons infected with hepatitis C virus. *Cell. Mol. Gastroenterol. Hepatol.* **2**, 676–684. (doi:10.1016/j.jcmgh.2016.05.012)
 105. Bengsch B, Thimme R, Blum HE. 2009 Role of host genetic factors in the outcome of hepatitis C virus infection. *Viruses* **1**, 104–125. (doi:10.3390/v1020104)
 106. Matsuura K, Tanaka Y. 2016 Host genetic variants influencing the clinical course of hepatitis C virus infection. *J. Med. Virol.* **88**, 185–195. (doi:10.1002/jmv.24334)
 107. Schmidt J, Thimme R, Neumann-Haefelin C. 2011 Host genetics in immune-mediated hepatitis C virus clearance. *Biomark Med.* **5**, 155–169. (doi:10.2217/bmm.11.19)
 108. Snaith A, El-Omar EM. 2008 *Helicobacter pylori*: host genetics and disease outcomes. *Expert Rev. Gastroenterol. Hepatol.* **2**, 577–585. (doi:10.1586/17474124.2.4.577)
 109. Linz B *et al.* 2007 An African origin for the intimate association between humans and *Helicobacter pylori*. *Nature* **445**, 915–918. (doi:10.1038/nature05562)
 110. Frenck RW, Clemens J. 2003 *Helicobacter* in the developing world. *Microbes Infect.* **5**, 705–713. (doi:10.1016/S1286-4579(03)00112-6)
 111. Malaty HM, Engstrand L, Pedersen NL, Graham DY. 1994 *Helicobacter pylori* infection: genetic and environmental influences. A study of twins. *Ann. Intern. Med.* **120**, 982–986. (doi:10.7326/0003-4819-120-12-199406150-00002)
 112. Figueiredo C *et al.* 2002 *Helicobacter pylori* and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. *J. Natl Cancer Inst.* **94**, 1680–1687. (doi:10.1093/jnci/94.22.1680)
 113. IARC. 2012 *Helicobacter pylori*. In *Biological agents, Monographs on the evaluation of carcinogenic risks to humans*, vol. 100B (pp. 385–435). Lyon, France: IARC.
 114. Graham DY, Lu H, Yamaoka Y. 2009 African, Asian or Indian enigma, the East Asian *Helicobacter pylori*: facts or medical myths. *J. Dig. Dis.* **10**, 77–84. (doi:10.1111/j.1751-2980.2009.00368.x)
 115. Shiotani A, Cen P, Graham DY. 2013 Eradication of gastric cancer is now both possible and practical. *Semin. Cancer Biol.* **23**, 492–501. (doi:10.1016/j.semcancer.2013.07.004)
 116. Smith S, Hughes J. 2007 Microsatellite and mitochondrial DNA variation defines island genetic reservoirs for reintroductions of an endangered Australian marsupial, *Perameles bougainville*. *Conserv. Genet.* **9**, 547. (doi:10.1007/s10592-007-9368-1)
 117. Woolford L, Bennett MD, Sims C, Thomas N, Friend JA, Nicholls PK, Warren KS, O'Hara AJ. 2009 Prevalence, emergence, and factors associated with a viral papillomatosis and carcinomatosis syndrome in wild, reintroduced, and captive western barred bandicoots (*Perameles bougainville*). *EcoHealth* **6**, 414–425. (doi:10.1007/s10393-009-0258-5)
 118. Janecka JE *et al.* 2017 Range-wide snow leopard phylogeography supports three subspecies. *J. Hered.* **108**, 597–607. (doi:10.1093/jhered/esx044)
 119. Joslin JO *et al.* 2000 Viral papilloma and squamous cell carcinomas in snow leopards (*Uncia uncia*). Paper presented at American Association of Zoo Veterinarians (AAZV) and International Association for Aquatic Animal Medicine (IAAAM) Joint Conference, New Orleans, USA.
 120. Acevedo-Whitehouse K, Gulland F, Greig D, Amos W. 2003 Disease susceptibility in California sea lions. *Nature* **422**, 35. (doi:10.1038/422035a)
 121. Browning HM, Acevedo-Whitehouse K, Gulland FM, Hall AJ, Finlayson J, Dagleish MP, Billington KJ, Colegrove K, Hammond JA. 2014 Evidence for a genetic basis of urogenital carcinoma in the wild California sea lion. *Proc. R. Soc. B* **281**, 20140240. (doi:10.1098/rspb.2014.0240)
 122. Spurgin LG, Richardson DS. 2010 How pathogens drive genetic diversity: MHC, mechanisms and

- misunderstandings. *Proc. R. Soc. B* **277**, 979–988. (doi:10.1098/rspb.2009.2084)
123. Újvári B, Madsen T, Kótenko T, Olsson M, Shine R, Wittzell H. 2002 Low genetic diversity threatens imminent extinction for the Hungarian meadow viper (*Vipera ursinii rakosiensis*). *Biol. Conserv.* **105**, 127–130. (doi:10.1016/S0006-3207(01)00176-8)
124. Hoffmann AA, Sgro CM. 2011 Climate change and evolutionary adaptation. *Nature* **470**, 479–485. (doi:10.1038/nature09670)
125. Pauls SU, Nowak C, Bálint M, Pfenninger M. 2013 The impact of global climate change on genetic diversity within populations and species. *Mol. Ecol.* **22**, 925–946. (doi:10.1111/mec.12152)
126. Jacqueline C *et al.* 2017 Infections and cancer: the ‘fifty shades of immunity’ hypothesis. *BMC Cancer* **17**, 257. (doi:10.1186/s12885-017-3234-4)
127. Gomez-Raya L, Amoss MS, Da Y, Beattie CW, Ash O, Rauw WM. 2009 Role of selection and inbreeding on the incidence of cutaneous malignant melanoma in Sinclair swine. *J. Anim. Breed. Genet.* **126**, 242–249. (doi:10.1111/j.1439-0388.2008.00779.x)