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Tumor predisposition and cancer syndromes as models to study gene X environment interactions

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Abstract

Cell division and organismal development are exquisitely orchestrated and regulated processes. The dysregulation of the molecular mechanisms underlying these processes may cause cancer, a consequence of cell-intrinsic and/or cell-extrinsic events. Cellular DNA can be damaged by spontaneous hydrolysis, reactive oxygen species, aberrant cellular metabolism, or other perturbations that cause DNA damage. Moreover, several environmental factors may damage the DNA, alter cellular metabolism, or affect the ability of cells to interact with their microenvironment. While some environmental factors are well established as carcinogens, there remains a large knowledge gap of others owing to the difficulty in identifying them because of the typically long interval between carcinogen exposure and cancer diagnosis. DNA damage increases in cells harboring mutations that impair their ability to correctly repair the DNA. Tumor predisposition syndromes in which cancers arise at an accelerated rate and in different organs - the equivalent of a sensitized background - provide a unique opportunity to examine how gene–environment interactions (GxE) influence cancer risk when the initiating genetic defect responsible for malignancy is known. Understanding the molecular processes that are altered by specific germline mutations, environmental exposures and related mechanisms that promote cancer, will allow the design of novel and effective preventive and therapeutic strategies.

Subject categories

Biological sciences/Cancer/Cancer genetics [URI/631/67/68]; Biological sciences/Genetics/Mutation [URI /631/208/737]; Biological sciences/Cancer/Cancer prevention [URI /631/67/2195]; Biological sciences/Cancer/cancer screening [URI /631/67/2322]

Introduction

Whether two-thirds of all cancers are caused by the inevitable spontaneous accumulation of somatic (acquired) genetic mutations as a consequence of aging[1,2], or whether environmental carcinogens are responsible for most mutations and cause 70–90% of human cancers has been debated recently[3,4]. However, it is difficult to determine the relative contribution of endogenous (spontaneous) mutations and those caused by exposure to environmental carcinogens in different patients. Similarly it is difficult to distinguish association from causation[5], and thus to define which of the thousands of mutations detected in a tumor biopsy or even in non-malignant or pre-malignant tissue are functioning as cancer ‘driver’ mutations[6,7].

To overcome these challenges, we recommend the study of gene–environment interactions (GxE) in causing cancer in carriers of germline mutations that cause well defined tumor predisposition syndromes [G] (TPSs) and cancer syndromes [G]. In these individuals the underlying genetic alterations that initiate carcinogenesis are well defined and are present in every cell. Therefore, TPSs offer a uniquely powerful opportunity to investigate GxE

interactions that contribute to human cancer risk. They provide a ‘sensitized’ genetic background against which to identify agents in the environment, and mechanistic insight into how exposure to these agents promotes cancer type-specific risk. Thus, TPSs resemble and complement the unusual environmental exposures, documented over the past century in occupational or geographic settings that clearly identified high-level exposure to specific environmental agents as strong drivers of cancer risk and incidence[3–5].

The recent realization of the much more widespread impact of inherited pathogenic mutations in many cancers reflects the development of next-generation sequencing [G] (NGS), targeted NGS [G] (t-NGS), whole exome sequencing [G] (WES), whole genome sequencing [G] (WGS) and multiplex ligation-dependent probe amplification [G] (MLPA) assays that enable the simultaneous analyses of multiple genes in germline and tumor DNAs[8]. Several genes have been identified, that when mutated in the germline or in somatic cells confer a higher cancer risk[9–11]. The current ‘cancer gene census’ of these genes (https://cancer.sanger.ac.uk/census) includes > 1% of all human genes, with ~90% implicated in cancer by somatic mutations, another 20% implicated by germline mutations, often in association with a TPS, and 10% displaying both cancer-associated somatic and germline mutations.

Over 100 TPS have been described[9,10]. Most are caused by heterozygous germline mutations. Loss of heterozygosity (LOH), e.g. loss of the remaining wild-type allele, is usually observed in the tumors that arise in individuals affected by these syndromes: this is considered further proof of causality[9,10]. This article focuses on a small number of TPSs that involve different but mechanistically overlapping processes – DNA repair, microRNA processing, genome integrity, cell signaling, and mitochondrial regulated cellular processes (Table 1). As many of these TPSs also have known environmental components, they provide both distinct and interrelated new opportunities to explore GxE in cancer type-specific risk.

Herein, we outline several TPSs, their underlying genetics and the evidence for environmental contributions to cancer risk in order to highlight their potential relevance for understanding how and why cancer develops in the general population. Lastly, we discuss opportunities for prevention in light of our knowledge of GxE.

Environment, genetics and/or GxE.

Environment and GxE

The most devastating localized cancer epidemic ever described occurred in 3 villages in Cappadocia in Turkey where over 50% of the population died of mesothelioma[12,13]. By comparison, the infamous Spanish influenza killed ‘only’ ~20% of the exposed population. Mesothelioma has been used for decades as the example of an environmentally-induced malignancy because its incidence rose exponentially following the massive use of asbestos fibers [G][14] during and after World War II[15,16]. Nevertheless, only a fraction of heavily exposed workers developed mesothelioma: for example, among asbestos miners who had worked for over 10 consecutive years in South African amphibole-asbestos mines, only ~4.6% developed mesothelioma[17].

In Cappadocia, erionite, a fiber similar to asbestos, has been linked to the mesothelioma epidemic[12,13]. In these villages, erionite present in the material used to build homes and dirt roads is inhaled and causes mesothelioma[18]. These findings were puzzling: why was the incidence of mesothelioma in Cappadocia so high? Was it because erionite is a much more potent carcinogen than asbestos? If so, why was there an excess of mesothelioma and not lung and laryngeal cancers - also caused by asbestos - especially since most of the male villagers were smokers?[12,13]. Moreover, most villagers were born, raised and died in these villages, so all of them were exposed for decades to the carcinogenic erionite, yet only 50% of them died of mesothelioma. Why then did the other 50% of the population not develop mesothelioma? And why did the incidence of mesothelioma remain at ~50% among villagers who emigrated abroad in their childhood?[12,13]

Studies of the epidemic in Cappadocia led to the discovery that susceptibility to mesothelioma was transmitted in a Mendelian fashion across multiple generations[19] and to the proposal that it was caused by a GxE interaction[12,13]. In subsequent investigations in US families with a similarly high incidence of mesothelioma but no detectable exposure to asbestos, it was discovered that heterozygous pathogenic germline mutations in the BRCA1-associated protein 1 (*BAP1*) tumor suppressor gene caused the ‘BAP1 cancer syndrome’ (Table 1) characterized by familial clustering of mesothelioma and uveal melanoma (UVM)[20–23], including bilateral UVM[24], and, although less frequently, by other malignancies[16,21,25–27,28,29].

In vitro experiments revealed that primary fibroblasts derived from carriers of heterozygous *BAP1* mutations and primary human mesothelial cells from BAP1 wild-type donors with down-regulated BAP1 expression were more susceptible than control BAP1 wild-type cells to the carcinogenic effects of ionizing radiation (IR), ultraviolet (UV) light and asbestos[30]. Furthermore, 36% of heterozygous *Bap1*-mutant ($Bap1^{+/-}$) mice when exposed to low doses (0.5 mg) of asbestos developed mesothelioma compared with 8.0% of wild-type littermates[31]. In parallel, in the control groups not exposed to asbestos, 3% of *Bap1*-mutant mice developed spontaneous mesothelioma but wild-type littermates did not[32]. Taken together these are clear indications of a GxE: the combined presence of a germline genetic variant and exposure to asbestos fibers together modulate a higher risk of disease than either component alone[31,32].

Genetics and GxE

In other instances, the genetic component responsible for familial cancer epidemics has been discovered first. Individuals with inherited, biallelic *BLM* and *WRN* mutations have Bloom (BS) and Werner syndrome (WS), respectively, which are autosomal recessive disorders that predispose to many cancer types. The *BLM* and *WRN* genes encode different RECQ DNA helicases [G]. RECQ helicases are known as the ‘caretakers of the genome’ that ensure genomic stability by modulating DNA replication, recombination, repair, transcription, and telomere maintenance[33,34]. Increased breaks and gaps in DNA occur spontaneously in BS and WS cells, as well as telomeric associations (fusions) of homologous chromosomes. These mutations are associated with hypersensitivity to many different chemical classes of

common DNA damaging agents, such as DNA topoisomerase I inhibitors, DNA cross-linking agents and radiation[35,36].

WS and BS provided some of the first and strongest evidence to support Boveri's hypothesis that cancer is a genetic disease[37]. Patients with WS, in addition to their characteristic prematurely aged appearance, have an elevated risk of cancer with 22% developing multiple malignancies[38]. A study of the first 100 cancers observed in individuals in the BS registry showed that 71 of 168 affected individuals developed cancer at a mean age of 24. Several of them developed as many as five independent cancer types; however, some did not develop cancer[39]. Moreover, heterozygosity for BLM^{ASH}, a founder mutation present in 1 in 100 individuals with Ashkenazi Jewish ancestry, may mildly increase the risk of colorectal cancer[40]. Mouse models carrying heterozygous mutations of the adenomatous polyposis coli (*Apc*) tumor suppressor and *Blm* genes, develop an increased number of intestinal tumors compared with wild-type controls[41]. Together, these observations suggest that the interaction of exposure to environmental carcinogens and constitutional genetics modulate cancer risk.

Table 1 includes examples of recessive TPSs in which genomic instability and the rate of stochastic events – mutagenesis – can be driven by environmental exposure-dependent DNA damage that, when un- or mis-repaired, may lead to mutations.

Key mechanisms

The existence of several TPSs that are caused by germline defects in DNA damage response (DDR) genes highlights the critical role of DNA repair in cancer[42] (Figure 1). Cancer incidence in carriers of pathogenic DDR mutations can be exacerbated by exposure to environmental carcinogens that induce genomic instability directly, for example, IR and UV light[30], or indirectly via chronic inflammation, for example, asbestos and chronic infections[16,43–46]. These same carcinogens can induce cell death, a physiological mechanism that eliminates the risk that cells that have accumulated DNA damage propagate and give rise to cancer[30,31]. The importance of cell death in cancer is underscored by the observation that cancer cells are more resistant than normal cells to regulated cell death often owing to alterations in the mitochondrial control of this process[47]. Mitochondrial alterations may also induce a metabolic switch from mitochondrial respiration [G] to aerobic glycolysis (Warburg effect; Box 1). Cancer growth is facilitated by aerobic glycolysis that provides the building blocks required for rapid cell proliferation and allows tumor cell growth in a hypoxic environment[48,49,] (Figure 2). Accordingly, mutations in genes that regulate either the DDR, cell death or cell metabolism account for most TPSs.

Highly penetrant germline mutations

Mutations in the genes encoding p53[50] and BAP1[22,31,32] are powerful inducers of cancer in humans and mouse models largely because they simultaneously impair DNA repair by homologous recombination [G] (HR)[50,51], cell death[30,52,53] and mitochondrial respiration[54–56] (Box 1). Heterozygous dominant mutations of *TP53* and *BAP1*, cause the Li-Fraumeni syndrome (LFS)[57–59] (Table 1), and the *BAP1* cancer syndrome[20,21] (Figure 2), respectively. *TP53* and *BAP1* heterozygous mutations appear to facilitate LOH, since tumor cells characteristically show bi-allelic inactivating mutations that in the case of *TP53,*

may include dominant-negative mutations[60,61]. Because *TP53* and *BAP1* heterozygous germline mutations cause cancer in close to 100% of mutation carriers, they are usually referred to as cancer syndromes. *TP53*-mutation carriers exhibit an ~85-fold risk of developing multiple cancers[57–59]; multiple cancers are also frequent in *BAP1*-mutation carriers[16,28,29]. However, there are some notable differences. Breast cancer, brain tumors, sarcomas and adrenocortical carcinomas are the most common cancers in patients with LFS[57–59], whereas mesothelioma, UVM, cutaneous melanoma, and clear cell renal cell carcinoma (ccRCC) are most common in *BAP1* mutation-carriers[16,28,29]. Most cases of LFS are inherited, although 20% are caused by de novo mutations present in the patient's germline but not detected in their parents[62]. In contrast, all cases of BAP1 cancer syndrome defined to date reported high cancer incidence through multiple generations, some dating back to the 16th century[26]. Inactivating, somatic (acquired) *TP53* mutations are common in most carcinomas, while biallelic somatic *BAP1* mutations are frequent only in the same tumor types found in individuals affected by the BAP1 cancer syndrome, including ~90% of metastatic UVMs[63], >60 of mesotheliomas[64,65], and ~11% of ccRCCs[66,67].

The different tumor phenotypes caused by *TP53* and *BAP1* mutations underscore that the effects of many mutations are influenced by tissue type and species (e.g. human versus mice). Moreover, intragenic polymorphisms, mutations, polymorphisms of genes in the p53 regulatory pathway, DNA methylation, altered expression of microRNAs, copy number variation, telomere attrition, and exposure to environmental carcinogens, can all modify the LFS phenotype[68]. The *BAP1*-mutant phenotype is simpler, as nearly all pathogenic *BAP1* mutations are either truncating mutations[28,29] with loss of the nuclear localization signal situated near the carboxy-terminus of BAP1 or, less frequently, are mutations in the catalytic domain that impair the ability of BAP1 to auto-deubiquitylate itself, a process required for BAP1 nuclear translocation[28,29,69]. Therefore, *BAP1* mutations redirect mutant BAP1 proteins to the cytoplasm where they are degraded[16,70].

Humans or mice harboring *TP53* or *BAP1*-mutations are extremely susceptible to the carcinogenic effects of IR[30,71], UV radiation[30,72], asbestos[30,31,73], and patients with LFS to tobacco-related carcinogenesis[74]. Analysis of dermal-derived fibroblasts or lymphocytes from patients with LFS harboring *TP53* heterozygous mutations revealed striking differences from normal cells in terms of chromosomal stability, apoptotic response to IR, G2 arrest after DNA damage, and gene expression profiles[75]. Similar to *BAP1* mutations, analysis of *TP53* mutations showed a connection between UV exposure, DNA damage, and skin carcinogenesis including melanoma[76]. Heterozygous *Trp53*-mutant mice have greatly increased susceptibility to UV-induced skin cancer, with homozygous *Trp53* knockout mice even more susceptible[77]. Both p53 and BAP1 activity eliminate precancerous cells in response to DNA damage. When this response is reduced by a *TP53* or *BAP1* mutation, UV, IR and asbestos exposure can induce clonal expansion of the mutated cells with a higher risk of overt cancer formation[30,72]. Accordingly, *Trp53*-heterozygous mice[77] and primary patient-derived LFS and *BAP1*-mutant cells exhibit reduced UV- and IR-induced cytotoxicity and apoptosis[30,78]. The frequency of spontaneous tumors is greatly enhanced by exposing p53-deficient mice to a single dose of IR[79], and radiation-associated secondary cancers are common in patients with LFS[71,80].

Smokers with germline *TP53* mutations are at higher risk of lung cancer[81], and mice carrying a mutant *Trp53* transgene become sensitive to cigarette smoke[74]. These mutant mice showed a significant age-related increase of unrepaired DNA adducts. Moreover, whereas wild-type mice exhibit a significant increase in apoptotic cells in the bronchial epithelium, the mutant mice did not undergo extensive cigarette smoke-induced apoptosis, indicating that the loss of p53 contributes to genomic instability by permitting inappropriate survival of cells that would normally undergo apoptosis following DNA damage[74]. Similar results were obtained in p53-mutant versus wild-type mice treated with the tobacco-related carcinogens benzo[a]pyrene or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone[82]. Moreover, benzo[a]pyrene–DNA adducts were found at a higher frequency in the liver and kidneys of p53-null mice, indicating that xenobiotic metabolism might also be influencing GxE in other organs[83]. Further underscoring GxE, aflatoxin B1, a food contaminant and potent hepatocarcinogen, is capable of immortalizing skin fibroblasts from patients with LFS but not cells from *TP53* wild-type individuals[84].

Different DNA repair mechanism defects underscore GxE in carcinogenesis.

Nucleotide excision repair [G] (NER) includes several pathways by which cells repair or bypass large DNA adducts that distort the DNA backbone and block transcription[85]. The importance of NER damage recognition mechanisms is exemplified by two hereditary diseases: xeroderma pigmentosum (XP) and Cockayne syndrome (CS)[86]. XP individuals have a >10,000-fold risk of developing squamous cell carcinoma (SCC) and melanoma when exposed to sunlight[87]. Intriguingly, CS is not associated with cancer (Table 1).

The initial damage recognition proteins of global genome repair [G] (GGR), xeroderma pigmentosum complementation group C (XPC) and DNA damage binding protein 2 (DDB2 also named XPE) bind to damage that disrupts base pairing within DNA (part of the GGR pathway). CS proteins (CSA & CSB) and UV-sensitive syndrome protein (UVSSA) relieve arrested RNA polymerase II at sites of damage as part of transcription-coupled repair [G] (TCR). Subsequently, the GGR and TCR pathways converge on a common pathway that involves incision with damage removal, re-synthesis and ligation to restore the DNA damage site. Mutations in genes encoding the components of this common downstream pathway, *XPB, XPD, XPA, XPF,* and *XPG,* are associated with diseases such as trichothiodystrophy [86] (Figure 3). Only biallelic mutations in XPC and other genes encoding proteins involved in NER have disease consequences.

Patients with XP with mutations in the *XPC* or *XPE* genes retain active TCR but show elevated mutation frequencies that lead to SCC and melanomas following sun exposure[88]. The UV-specific mutations in SCCs originate from unrepaired UV photoproducts in non-transcribed genome regions and the non-transcribed strands of expressed genes[88]. However, SCCs from patients carrying mutations in *XPC* show no increased mutations in transcribed strands. Therefore, efficient TCR does not protect against SCC formation in patients with mutated *XPC*.

Patients with CS with mutations in the Cockayne syndrome-type A (*CSA*; also known as *ERCC8*) or *CSB* (also known as *ERCC6*) genes have reduced TCR and display a wide range of developmental and neurological symptoms, though do not develop cancer despite severe

photosensitivity[89]. Cells from patients with CS *in vitro* show no elevation of UV-induced mutagenesis[90]. A related, mildly photosensitive disease, ultraviolet sensitive syndrome (UVS), also characterized by a deficiency in TCR, is associated with mutations in the gene UV-stimulated scaffold protein A (*UVSSA*) or occasionally *CSA* or *CSB,* but has no developmental or neurological symptoms. Patients homozygous for this mutation do not develop skin cancers[91]. *In vitro* analysis of primary cells with mutations in *CSA*, *CSB* or *UVSSA* revealed that they are essentially identical in sensitivity to most transcription-blocking DNA damage, but differ in their response to reactive oxygen species (ROS)[92,93]. Whereas cells mutant in *CSA* or *CSB* are sensitive to ROS, cells with mutations in *UVSSA* are not, suggesting that the development and neurological pathologies have their origins in an altered response to ROS.

Mutation avoidance in CS is postulated to occur through arrested transcription that generates an R-loop, consisting of separated DNA strands and a nascent mRNA strand hybridized to the template strand[94,95]. R-loops lead to S phase arrest with activation of ataxia telangiectasia mutated (ATM), the DNA damage transducing kinase that causes a delay in DNA replication until damage is removed from the template strand and transcription resumes[96,97]; if the damage is not repaired, cell death is triggered. Resumption of replication signals that DNA repair was successful with no concomitant mutagenesis[94,95]. The delay in replication in cells from patients with CS prevents replication with the creation of mutations, explaining the absence of tumors in UV-damaged skin from patients with CS.

The involvement of an ATM-dependent signaling pathway in CS is likely to cause variations in signaling according to cell type and species that confer different levels of avoidance of mutagenesis and carcinogenesis. For example, transfection of plasmids that contain DNA damage into cells from patients with XP or CS results in elevated mutations in the plasmids, suggesting that the damaged plasmid does not induce an ATM-dependent replication delay in either cell type[98]. In contrast, rodent cells and mice with CS-type mutations exhibit increased mutagenesis and increased cancer incidence[99,100]. Since rodent cells naturally have much reduced GGR, mutation of the rodent *Csa* or *Csb* genes effectively creates rodents with defects in both GGR and TCR leading to greater mutagenesis and cancer incidence after UV irradiation[100]. These data underscore how differences in DNA repair mechanisms among species can significantly influence environmental carcinogenesis.

Mutations of different genes along the same pathway can lead to the same TPS

Lynch syndrome (LS) is the most common autosomal dominant TPS. It is caused by germline mutations of several DNA mismatch repair (MMR) genes[101] (Table 1). The role of MMR is to repair base misincorporation errors made during DNA replication by the replicative DNA polymerases, thus preventing these errors from becoming fixed as mutations. Therefore, LS is characterized by high mutation rates leading to cancer[102]. The mutS homolog 2 (MSH2)–MSH6 complex primarily recognizes base–base mispairs and small insertion or deletion mispairs, whereas the MSH2–MSH3 complex more broadly recognizes insertion or deletion mispairs as well as some single base mispairs[103,104]. The two heterodimers, MSH2–MSH6 and MSH2–MSH3, in the presence of ATP and a mispair, recruit MutLα a third heterodimer of the mutL homologue 1 (MLH1) and postmeiotic

segregation increased 2 (PMS2) proteins with activation of an intrinsic endonuclease that makes a strand-specific, single strand break in DNA. Mispair excision can then be initiated by exonuclease 1 (exo1), although exo1-independent mispair excision mechanisms exist[105]. Mutations in the MMR genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*) impair the function of their encoded proteins, altering their recognition and repair of mismatched nucleotides and of insertion or deletion loops[101].

Patients affected by LS account for about 3%−5% of all colorectal cancers[106]. In addition, LS carriers have a higher risk of developing many other different cancer types. Their lifetime risk of developing endometrial cancer is estimated at 27%−71%, cancers of the stomach and ovary at 2%−13%, and lower frequencies for other cancer types but still elevated above the risk for normal individuals[107]. The clinical expression of LS is geographically variable: LS families in Asia develop stomach cancer more frequently than families in Western countries, pointing to differences in GxE in determining the tumor phenotype[108,109]. The penetrance [G] of LS varies substantially depending on the person's gender, which MMR gene is mutated, and is highly variable across carriers with mutations in the same MMR gene[101]. These variations suggest that environmental factors, or possibly additional genetic variants, play a critical role in tumor development in LS. Dietary and lifestyle factors that are known to be relevant in sporadic colorectal carcinogenesis influence the development of colorectal cancer in patients affected by LS[110,111], since it is possible to reduce its incidence by reducing chronic inflammation[112,113].

Fanconi anemia (FA) is an autosomal recessive (in rare instances X-linked recessive) DNA repair deficiency, characterized by hypersensitivity to DNA crosslinking agents[114,115] (Table 1). FA is linked to inherited biallelic inactivation of any one of 23 FA genes whose protein products are involved in DNA repair. The 23 FA proteins, along with FA-associated proteins (FAAPs), interact in a common cellular pathway to repair DNA interstrand cross-links [G] (ICLs) known as the FA pathway or the FA–BRCA pathway[114]. The pathway involves the detection of the DNA crosslink at the stalled replication fork, the excision of the crosslink, the local generation of a double strand break, and the use of HR proteins downstream to repair the break. Disruption of the FA pathway results in chromosome instability, sensitivity to DNA cross-linking agents, and the clinical features of FA. Cancer is linked to the increased susceptibility of patients with FA to the DNA-damaging action of environmental carcinogens, including IR, UV light and chemotherapeutic agents[114,115]. Based on mouse modeling, it can be predicted that patients with FA have an increased sensitivity to DNA damage generated by intrinsic and environmental aldehydes[116,117]. Aldehydes may have an intrinsic source, resulting from normal metabolism, or may have an extrinsic source, such as from the diet or from alcohol consumption. Formaldehyde, for example, is a naturally occurring compound, and humans produce it as part of normal metabolic pathways. Also, formaldehyde can be inhaled, rapidly metabolized, and exhaled as carbon dioxide[114,115]. Patients with FA are strongly predisposed to head and neck squamous cell cancers, many of which originate in the oral cavity and, accordingly, these patients are advised to limit their environmental aldehyde and alcohol exposure. However, the relative contribution of human papillomavirus (HPV) infection, another potential co-carcinogen versus these other environmental exposures remains to be defined[118,119]. Finally, patients with FA who carry the common dominant-negative allele of the aldehyde-catalyzing enzyme aldehyde

dehydrogenase 2 (ALDH2) (the ALDH2*2 or alcohol-induced flushing variant) have a deficiency in aldehyde clearance and a more severe and rapidly progressive disease course with an acceleration of bone marrow failure[120]. The clinical manifestations of these patients further underscore the importance of the FA pathway in repairing aldehyde-associated DNA damage.

Tumors in patients with tuberous sclerosis complex (TSC; an autosomal dominant disease) develop because of inactivation of both alleles of either *TSC1* (also known as hamartin) or *TSC2* (also known as tuberin)[121,122], with the germline mutation inactivating one allele of *TSC1* or *TSC2* and a somatic event inactivating the remaining wild-type allele (Table 1). TSC1 and TSC2 form a complex that negatively regulates mTOR complex 1 (mTORC1), a master regulator of cellular growth and metabolism[122,123]. Loss of function of the TSC1–TSC2 complex results in aberrant activation of mTORC1, which promotes the synthesis of lipids, nucleotides and proteins while inhibiting autophagy[123]. Facial angiofibromas in patients with TSC represent one of the most compelling examples of GxE in inherited TPSs. Tyburczy et al.[121] found that of the somatic point mutations identified in fibroblasts from skin tumors from patients with TSC, 50% were CC>TT UV 'signature' mutations, which have never been observed as germline mutations in TSC. These results implicate UV-induced DNA damage as a cause of second-hit mutations and the development of facial angiofibromas, and suggest that measures to limit UV exposure may reduce these often disfiguring tumors found in ~80% of patients[121]. The wide range of tumors in other organs suggests that environmental factors could play a broader role in TSC, but this is not yet proven. For example, the number of renal angiomyolipomas tends to be similar between the two kidneys of an individual patient, but varies widely between patients, even within family members carrying the same germline mutation (E.P.H., personal observation).

Eker rats carry a heterozygous *Tsc2* germline mutation, and were the first instance of a dominantly-inherited cancer predisposing gene identified in a naturally occurring animal model. Eker rats develop renal preneoplastic and neoplastic lesions[124], and are highly susceptible to renal carcinogens (such as dimethylnitrosamine). Eker rats were used to show that GxE during development can enhance the penetrance of a tumor suppressor gene defect in the adult. This is different from 'traditional' GxE that facilitate or inhibit the acquisition of additional somatic mutations required for tumorigenesis[125].

The finding that mutations of different genes along a specific pathway produce the same TPS, as shown in the three examples reviewed above, underscore the importance of elucidating mechanisms to identify common preventive and therapeutic approaches to which carriers of these mutations may be most susceptible (see below).

Evidence of GxE in all TPSs

For several germline mutations associated with increased cancer risk, the possible role of GxE remains to be investigated. For example, patients with Birt-Hogg-Dubé syndrome (BHD) (Table 1), an autosomal dominant inherited disorder caused by germline mutations in the folliculin (*FLCN*) gene[126], develop renal cancers subsequent to inactivation of the wild type allele in 12%−34% of affected patients at the early age of 46–52[126,127]. Individuals

within families who share the same *FLCN* alteration or between families who harbor the same *FLCN* mutation may or may not develop renal cancer, or the benign cutaneous and pulmonary manifestations associated with this syndrome. These observations suggest that environmental factors likely contribute to the phenotypic heterogeneity observed in BHD.

Similarly, individuals affected by the autosomal dominant hereditary 'DICER1 syndrome' (Table 1) can develop one or more tumor types, mostly rare cancers occurring in the pediatric and adolescent age ranges[128]. However, most mutation carriers never develop cancer. As some DICER1 syndrome-associated tumors arise in utero,[129] post-natal environmental influences are likely minimal in these cases. However, factors that regulate DICER1 expression post-natally may influence the risk of lung cancer as well as other cancers associated with DICER1 syndrome[130]. For example, one study showed that macrophages from the lungs of smokers exhibited down-regulation of multiple miRNAs, which was mediated by SUMOylation [G] of DICER1[131].

Studying GxE in cancer risk

The variable occurrence of cancer in TPS pedigrees provides the opportunity to use pathogenic TPS variants to anchor the search for additional genetic modifiers or environmental exposures that drive cancer risk[132]. The rapidly developing field of mutational signatures[121,133] is one example of a powerful new approach to assess genetic and environmental contributors to cancer risk in TPSs, as well as in the general population. Specific mutational signatures (recurrent mutation types or patterns) have been strongly associated with germline variants in TPSs[134–137] that modify DNA repair pathways and with the mutational consequences of exposure to DNA-damaging environmental agents such as UV light[138], tobacco carcinogens[139] and environmental toxins[138]. Additional approaches to characterize an individual's 'exposome' - the diversity and amount of all exposures, from conception to death[140–146] - should help better define individual cancer incidence or cancer type-specific risk as a function of genotype. Alterations in global and gene-specific methylation have also been linked to environmental exposures to carcinogens[143–145]. By modulating gene expression, alterations in gene methylation may contribute to carcinogenesis, especially those that occur during the prenatal period and childhood, because they appear more stable than those occurring later in life[145]. Therefore, the carcinogenic effects of environmental pollutants may be influenced by the age at which the exposure occurs. This may account, at least in part, for observations in which genetically predisposed individuals who were exposed to environmental carcinogens for a relatively brief period of time early in life, had the same incidence of cancer as those exposed for their entire life[12,13].

Exposure and mechanism revealing assays of the types described above have the potential to better define the contribution of exposure-associated mutagenic and epigenomic contributions to population-level cancer risk, as well as cancer type- and tissue-specific risks[134,138,147]. These exciting possibility are being further enabled by the assembly of large, epidemiologically well-defined and characterized populations as part of the 100,000 Genomes[148], the UK Biobank[149,150] and All of Us[151] Projects, and the growing assemblies of large, well-documented cancer resources provided by TCGA, ICGC and related projects.

Conventional wisdom states that gene mutations cause or predispose to cancer. What if some mutations are instead protective? One might imagine so, and conceivably, those genes might function not only in immunity but also in the development of tumor vasculature, the promotion of metastasis, and other known processes in the pathogenesis of cancer. Inbred mice allow us an opportunity to identify host factors that confer resistance, as well as susceptibility to cancer. Ninety-nine percent of human genes have homologs [G] in mice, and 80% have orthologs [G]; moreover, 90% percent of the mouse genome exists in segments in which the gene order has been conserved with that in the human genome[152]. Thus, many discoveries made using mice have had corresponding implications in humans. Using a mouse mutagenesis protocol in which germline mutations are randomly induced with a chemical mutagen (http://mutagenetix.utsouthwestern.edu), an unbiased forward genetic approach (from phenotype to gene) has been developed to facilitate the understanding of the genetic basis of human biology and disease, including cancer[153]. Using this approach, mice that show variant phenotypes are created by injecting animals of the initial G0 generation with the chemical N-ethyl-N-nitrosourea (also known as ENU), a powerful mutagen for mouse spermatogonial cells[154]. The mutational causes of phenotypes are determined computationally, by automated meiotic mapping performed concurrently with phenotypic screening (Figure 4). In this way, the molecular cause of a newly observed phenotype can be established in real time[153,155].

This provides the stage for the more demanding task of using forward genetics to identify genes and mutations that suppress disease phenotypes (Figure 4). Proteins encoded by genes that harbor suppressive alleles once identified, might then be pursued as drug targets[153]. For example, the central role of interleukin-33 (IL-33) signaling in the pathogenesis of myeloproliferative neoplasms (MPNs) was discovered because the genetic ablation of the IL-33 signaling pathway was sufficient and necessary to restore normal hematopoiesis and abrogate MPN-like disease in mice lacking SH2 domain-containing inositol 5’-phosphatase (SHIP)[156]. Additionally, in the transgenic Janus kinase 2 (*JAK2*)^{V617F} (a mutation often found in BCR–ABL1–negative MPNs) mouse model, the onset of MPN was delayed in animals lacking IL-33 in radiation-resistant cells[156]. The identification of cancer resistance genes in this way is likely just a beginning, as saturation of the germline genome remains at less than 5% (B.B. personal observation).

Taken together, GxE seen in TPSs are much easier to study in mice than in humans. In mice, environmental and genetic variables are largely controllable. This includes control of the microbiome if necessary, through generation of gnotobiotic mice. Nonetheless, some tumors and some environmental conditions exist only in humans. A unified approach may be the best, wherein TPSs detected in mice are actively sought in human populations, and mouse models of human TPSs are actively created to study mechanisms and for preclinical studies.

Opportunities for prevention and therapy

Mechanistic insight into the contributions of individual genetic and environmental components is providing vital information to design preventive and targeted therapeutic approaches at the individual and at population-level.

The increased susceptibility of *TP53*$^{+/-}$, *BAP1*$^{+/-}$ and *XPC*$^{-/-}$ mutation carriers to environmental carcinogens justifies measures to eliminate or reduce known, cancer-associated exposures in order to prevent or delay cancer onset. This may include avoiding certain jobs and living in geographical areas that are likely to be associated with low asbestos exposure or less intense sun exposure. Radical measures to prevent mesothelioma in genetically predisposed individuals were taken in Cappadocia, where two new erionite-free villages were built and villagers relocated[12,13].

Moreover, enrollment in early detection cancer screening programs and the parallel implementation of preventive measures, such as screening with ultrasound and magnetic resonance imaging (MRI), rather than computed tomography (CT) imaging to diminish the risk of cancer caused by diagnostic IR, together with surgical removal of pre-malignant lesions and of early-stage tumors, has significantly increased survival in for example, patients with LS[157–159], *BRCA1* or *BRCA2* mutations[160], or LFS[58,161,162]. Thus, patients with LS or LFS and *BRCA1* or *BRCA2* carriers, once identified, can begin these potentially life-saving procedures. Similar data for other syndromes are becoming available and support the widespread value of preventive or early detection programs[16]. For example, several patients with *BAP1*-mutations enrolled in screening programs were diagnosed with melanoma and cured by surgical excision, and others diagnosed with very early-stage mesothelioma exhibited long-term survival[16,163]. Although the prolonged survival - 5–10+ years for mesotheliomas occurring in carriers of germline *BAP1* mutations, versus 1 year in sporadic mesothelioma[16] - may be partly related to screening and early detection, better survival in patients carrying germline *BAP1* mutations predates the discovery of the *BAP1* cancer syndrome, pointing to differences in tumor biology and/or the microenvironment[164,165].

Individuals with germline *TP53* mutations have increased oxidative metabolism[55] (Box 2). Amongst its various metabolic effects, metformin inhibits mitochondrial respiration [G]. The pharmacological attenuation of mitochondrial function in a mouse model of LFS using metformin at a therapeutic dose equivalent to that used in humans resulted in a 22% increase in cancer-free survival (n=21 mice), suggesting that external modulation of mitochondrial metabolism in LFS could be beneficial for cancer prevention[166]. In a proof-of-concept clinical study, treating patients with LFS with metformin decreased mitochondrial function in their blood and muscle cells and induced biomarkers similar to those associated with increased survival in the mouse model of LFS[166]. Furthermore, it would be worthwhile to investigate whether patients with LFS benefit from metformin and mild hypoxia that concomitantly decreases respiration and oxygen toxicity.

The *TP53*^{R337H} mutation present in ~0.3% of the population of Southern Brazil[167,168], gives rise to a form of LFS frequently characterized by pediatric adrenocortical carcinoma. The R337H residue substitution is in the C-terminal oligomerization domain of p53 and is thought to decrease the stability of the active form of p53, a homotetramer, in a pH-dependent manner[169]. Although the *Trp53*^{R334H} mouse model (homolog of human *TP53*^{R337H}) did not have increased cancer incidence, exposure to the environmental carcinogen diethylnitrosamine increased liver carcinogenesis in association with decreased p53 oligomerization[167,168,170]. The adrenal glands have a high tissue concentration of

ascorbic acid (vitamin C) and, notably, *TP53*^{R337H} carriers have decreased plasma ascorbate levels due to increased oxidative stress[171]. Thus, mutant p53 oligomerization in the adrenal glands of R337H mutation carriers might be further compromised by vitamin C deficiency. It is tempting to speculate that environmental changes, such as alterations in dietary vitamin C intake or lactate production by inhibition of respiration with metformin, may affect p53 activity and cancer development. The presence of *TP53* and *BAP1* mutations may also help inform therapy: defective DNA repair leads to chromosomal instability and higher mutational load[30,172], which potentially provides a rationale for patient stratification with regard to immunotherapy[16].

Mutagenesis is promoted by chronic inflammation-associated ROS production, and this may cooperate with inflammatory cell release of cytokines to promote tumor growth[173]. This knowledge led to chemo-prevention trials that demonstrated how daily aspirin intake, by reducing inflammation in the colon, significantly reduced the incidence of colon cancer in LS carriers[112,113]. Specifically, in the Colorectal Adenoma/carcinoma Prevention Program (CAPP2) randomized study, high doses of daily aspirin taken by patients with LS resulted in a 63% reduction in the relative risk of developing colorectal cancer[112]. Further support for the preventive effect of aspirin in cancer comes from experiments *in vitro* and *in vivo*[174,175,176]. The chemo-preventive activity of aspirin has been linked to its ability to simultaneously inhibit cyclooxygenase 2 (COX2) and high mobility group B1 (HMGB1) activities[43] and to its anti-proliferative and apoptosis-inducing activities[177]. These findings underscore the value of reducing the contributing role of environmental factors causing chronic inflammation to prevent cancer, especially in genetically predisposed individuals. Moreover, patients with LS may benefit from immunotherapy (programmed cell death protein 1 (PD1) and PD1 ligand 1 (PDL1) approaches) because of the very high mutation burden in their tumors[178].

The discovery of the links between the TSC1–TSC2 complex and mTORC1 activation in *Drosophila*122, represents another excellent example of how understanding basic signaling mechanisms can lead to high-impact advances in clinical practice. The role of TSC1 and TSC2 proteins in inhibiting mTORC1 led to studies that demonstrated a clinical benefit associated with the mTORC1 inhibitor sirolimus (rapamycin)[122]. Patients with TSC benefit from treatment with mTORC1 inhibitors (rapalogs, i.e. sirolimus and everolimus)[179], though their primarily cytostatic effect (the tumors regrow upon treatment discontinuation) requires lifelong therapy.

Recognition of the causative role of germline mutations in cancer initiation and tumor progression identifies these genes and mutations as high-value therapeutic targets. More detailed data may reveal specific genetic or metabolic vulnerabilities that could be harnessed to prevent or treat the associated cancer(s). Moreover, mutation-targeted therapies have a higher likelihood to be beneficial to carriers of pathogenic germline mutations where key pathogenic mutations and their consequences are known. Many clinical trials targeting specific pathways in different cancer syndromes are ongoing (for example, NCT03207347[180], NCT01981525[181] and NCT03448718[182]), and information from these trials will likely inform the use of similar therapies in sporadic malignancies carrying the equivalent acquired mutations.

Conclusions

Many – if not most – cancers are a consequence of GxE. The differential contribution of genes or environment is most obvious when one or the other component most strongly drives cancer risk. However, carcinogenesis is often a long process: spontaneous and environmentally-induced mutations can accumulate over the course of decades, with many cancers only becoming clinically overt 20 or more years after first carcinogen exposure[16,139,183–185]. This long timespan for most cancers makes it difficult to clearly identify ‘causative’ mutations, and the timing of critical mutational events, or strongly promoting environmental exposures.

Recent data indicate that about 12% of cancers develop in carriers of pathogenic germline mutations, mostly of genes that regulate DNA repair and cell death[186–188]. This percentage is likely to grow with additional analyses of cancer patients and experimental forward genetics studies of cancer predisposition in mice. These germline mutations might accelerate the accumulation of DNA damage as cells divide with age, and/or in response to environmental mutagen or carcinogen exposure. TPSs offer the unique opportunity to study cancer in a setting in which the initiating genetic event is known. LOH occurs in most of these malignancies, further proof of the key oncogenic role of these mutations in driving tumor growth. Many of these syndromes can lead to tumors in multiple organs, allowing GxE to be addressed in multiple cellular contexts within a defined genetic background. A subset of these exposures may be identifiable by virtue of their ability to generate an agent or exposure-specific mutational signature[138].

The studies of GxE are helping us to solve the question of why some individuals do - and most do not - develop cancer when they have comparable exposures to any given carcinogen. Information on GxE allows us in turn to tailor prevention and early detection to those who need it the most. We need to identify the exposures and the mechanisms that make carriers of these mutations more susceptible to cancer and also to other diseases and develop and implement prevention strategies. At times this is simple and the information is already available. For example, recent discoveries linked specific mutations to increased individual susceptibility to various infectious agents: by avoiding travel in areas where these pathogens are prevalent, mutation carriers can reduce their risk of life-threatening infections[189,190]. Similarly, we have already accumulated a wealth of knowledge that allows us to start implementing lifesaving approaches for carriers of pathogenic germline mutations, as discussed in this article with respect to cancer (see, “Opportunities for Prevention and Therapy”). It is now time to translate this knowledge into preventive and early detection strategies to save lives on a larger scale. However, to make a global impact and reduce the cancer burden, we need widespread genetic testing to identify those who carry pathogenic germline mutations.

Access to germline testing varies depending on regional availability and insurance coverage. In the US, free germline genetic testing for patients with cancer and other diseases is offered in only a few institutions, and is otherwise unavailable or expensive and often not covered by health insurance. Therefore, presently we are not identifying most germline mutation carriers: these individuals are unaware of their increased cancer risk and susceptibility to

carcinogens. This creates an obvious yet unrecognized health disparity: many lives that could be saved from cancer are not. For example, the median age for colorectal cancer diagnosis for patients with LS and for breast cancer in *BRCA1* or *BRCA2* carriers is 45 years old, at or before the age at which colonoscopy and mammography screening, respectively are recommended. Therefore, many patients with LS and *BRCA1* or *BRCA2* carriers, among others, cannot benefit from surgery or therapy, unless the mutation is identified through screening at an earlier age.

To address this challenge, the Healthy Nevada Project (HNP)[191], sponsored by the State of Nevada and by Renown Health, is conducting free WES and providing free genetic counseling to an initial 125,000 individuals living in the state on a voluntary basis until the quota is reached. Sequencing may be extended to the entire State population depending on additional funding. Leveraging this unique resource with separate grant funding has allowed the HNP cohort to be investigated for evidence of GxE that may lead to preventive and early detection measures. It is anticipated that similar initiatives will soon be started elsewhere, and that genetic screening together with studies of GxE contributions to common adult cancers will help save lives, reduce health care costs and provide a major boost in our battle with cancer.

In summary, TPSs provide the opportunity to dissect key mechanisms and events in carcinogenesis, and the contributions of GxE that modulate cancer risk and the cancer phenotype. This knowledge in turn, is improving our ability to prevent cancer, to detect cancer at an early stage when it is often curable by surgical resection (melanoma, colon and breast cancer, etc.,), and to design specific therapies to target the mechanisms and interactions that give rise to cancer and that promote cancer progression.

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GLOSSARY:

Asbestos fibers

For regulatory purposes, 6 out of approximately 400 mineral fibers naturally present in the environment were collectively named ‘asbestos’ and their use prohibited or severely restricted in the past decades in the US, Australia and Western Europe. The remaining ~394 mineral fibers are not regulated and thus can and have been used causing human exposure and mesothelioma: among them erionite.

Base excision repair (BER)

This repair system removes single base damage from alkylating agents or reactive oxygen species. One branch consists of a glycosylase that cleaves the base-deoxyribose bond leaving an apurinic site that is subsequently cleaved and replaced by a small 1–2 base patch. Formation of a longer patch branch involves the activity of CSB, XRCC1 and PARP1.

Cancer syndrome

Those TPS in which close to 100% of carriers develop one or more cancers during their lifetime. Examples include Li-Fraumeni syndrome (~95% of women carriers develop cancer) and the BAP1 cancer syndrome (~100% of carriers develop cancer), which are caused by heterozygous autosomal dominant mutations of the *TP53* and *BAP1* genes, respectively.

DICER1

An endonuclease implicated in microRNA biogenesis and the specific regulation of mRNAs. This mainly cytoplasmic enzyme cleaves precursor hairpin microRNAs to produce mature microRNAs (known as 5’-miRNA and 3’-miRNA, one of which will be loaded onto the RNA Induced Silencing Complex (RISC), ultimately resulting in down-regulation or silencing of the targeted mRNAs.

DNA helicases

Enzymes that unwind the two strands of the DNA helix, a process needed for all aspects of DNA metabolism that in turn is important for DNA replication and repair.

DNA interstrand cross-links (ICLs)

Covalent bonds between bases on opposite strands of DNA.

Global genome repair (GGR)

A branch of NER that predominantly occurs in nontranscribed DNA and nontranscribed strands of expressed genes. Damage recognition involves two DNA binding proteins, XPE and XPC. Subsequent steps involving DNA unwinding, incision, polymerization and ligation are common to GGR and transcription-coupled repair (TCR).

Homologous recombination

This process is essential for the repair of double-stranded DNA breaks and consists of an exchange or replacement of a segment of parental DNA with a segment having the homologous sequence from a partner DNA.

Homologs
Genes related to second genes by descent from a common ancestral DNA sequence.

Mitochondrial respiration
Also referred to as oxidative phosphorylation (OXPHOS), is a process that takes place in the mitochondria and provides the major source of ATP in aerobic organisms.

Mitophagy
Autophagic removal of damaged mitochondria.

Multiplex ligation-dependent probe amplification (MLPA)
This is a multiplex polymerase chain reaction method used to detect larger DNA deletions and copy number variations, which are often missed by next-generation sequencing and Sanger sequencing.

Next generation sequencing (NGS)
A high throughput sequencing technique that allows rapid simultaneous sequencing of the DNA or RNA of multiple genes. Designed to detect nucleotide level mutations, it largely replaced manual Sanger sequencing, although this is used to confirm pathogenic mutations detected by NGS.

Non-homologous end joining (NHEJ)
An error prone DNA double strand break repair process that entails rejoining of DNA breaks without reliance on a homologous template.

Nucleotide-excision repair (NER)
The process by which ultraviolet light induced DNA lesions and other large adducts such as from AAF or B(a)P are repaired.

Orthologs
Genes in different species that evolved from a common ancestral gene by speciation. Usually, orthologs retain the same function in the course of evolution.

Penetrance
The likelihood that a person who has a certain disease-causing mutation in a gene will show signs and symptoms of the disease.

Spliceosome
Molecular complex involved in removing introns (intervening sequences between coding sequences) from the primary RNA transcript

SUMOylation
A process by which proteins are post-translationally modified, by the covalent addition of **S**mall **U**biquitin-like **Mo**difier proteins through lysine side chains, resulting in a remodeling

of the surface of these proteins, thereby affecting their function in three main ways: through inhibition of the usual interaction between the target of sumoylation and another protein, through provision of a new binding surface, and through conformational changes in the target protein.

Targeted NGS (tNGS)
These are commercial or custom gene panels that target the exons of specific sets of genes, for example all tumor suppressor genes.

Transcribed coupled repair (TCR)
A branch of NER that predominantly occurs on the transcribed strand of expressed genes. Damage recognition involves RNA polymerase II arrest at damage in transcribed strands that is relieved by the action of CSA, CSB, and UVSSA. Subsequent steps involving DNA incision, polymerization and ligation are common to GGR and TCR.

Tumor predisposition syndrome (TPS)
Affected individuals are predisposed to benign and/or malignant tumors. Depending on the gene that is mutated, a variable fraction of mutation-carriers develop one or more tumors during their lifetime. TPSs can be caused by heterozygous (autosomal dominant) or homozygous (autosomal recessive) mutations.

Whole exome sequencing (WES)
All exons in the genome are sequenced.

Whole genome sequencing (WGS)
All of the genome including introns is sequenced. Identifies both nucleotide level deletions and large DNA deletions but the interpretation of the data requires special expertise and the use of super-computers that can handle the very large amount of data.

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BOX 1.

The Warburg effect and mitochondrial metabolism

Metabolic reprogramming is a hallmark of cancer[195]. Otto Warburg found that, even in the presence of oxygen, cancer cells produced increased amounts of lactate which later was interpreted as cancer cells using enhanced metabolism of glucose by glycolysis to produce ATP (aerobic glycolysis), instead of the more energy-efficient oxidative phosphorylation (OXPHOS)[196]. Aerobic glycolysis provides cancer cells with different metabolites and varying oxidative or redox molecules required for rapid tumor cell proliferation, as well as the ability to grow in a hypoxic environment[49,197]. The presence of BRCA1-associated protein 1 (*BAP1*) mutations in otherwise normal cells also induces aerobic glycolysis[43]. *TP53* mutations cause an increase in OXPHOS in cells, confirmed in a mouse model (*Trp53*^{R172H}) of the human *TP53*^{R175H} mutation 'hotspot' in Li-Fraumeni syndrome and shown to be mediated by mutant p53 retention of mitochondrial regulatory activities[55]. While higher oxidative metabolic capacity is protective against cancer[198], increased mitochondrial capacity could also be detrimental by promoting cancer cell survival[199,200]. Crossing LFS mice with heterozygous polymerase γ (POLG) mutant mice, which have a mild mitochondrial deficiency and a normal lifespan, resulted in a 40% increase in cancer-free survival associated with specific anti-proliferative cell signaling changes[166].

The abnormal accumulation of mitochondrial metabolites that can operate as oncometabolites, including fumarate, succinate, and D-2-hydroxyglutarate (D-2HG), can promote malignancy[201]. Succinate dehydrogenase (*SDH*), fumarate hydratase (*FH*), and isocitrate dehydrogenase 2 (*IDH2)* can be affected by germline mutations[201,202]. *IDH1* and *IDH2* somatic mutations are found in several human tumors[203]. Carney-Stratakis syndrome (characterized by gastrointestinal stromal tumours and paragangliomas) and hereditary leiomyomatosis and renal cell cancer (HLRCC; an autosomal dominant disorder in which individuals are at risk of developing leiomyomas and kidney cancer), are caused by germline mutations of *SDH* and *FH*, respectively[202]. While *SDH* and *FH* are prone to loss-of-function mutations, accompanied by the accumulation of fumarate and/or succinate, *IDH1* and *IDH2* frequently display gain-of-function mutations, leading to the synthesis of D-2HG[204]. All of these oncometabolites share the capacity to inhibit α-ketoglutarate (α-KG)-dependent enzymes that are involved in fatty acid metabolism, oxygen sensing, and epigenetic modifications, which could primarily be affected by dietary composition and ambient oxygen availability in the environment[205–207]. In summary, perturbations of mitochondrial metabolism may favor tumor development.

BOX 2.

Reactive oxygen species

Reactive oxygen species (ROS) are genotoxins that favor the accumulation of DNA mutations and the activation of oncogenic signaling pathways[208]. Mitochondrial respiration produces ROS that influence cell proliferation, differentiation, and survival. Fanconi anemia (FA) genes, mutated or silenced in a large proportion of human tumors, regulate mitophagy [G], suggesting that at least part of the tumor suppressive activity of FA proteins may derive from the proficient removal of damaged mitochondria overproducing ROS[209]. Defects in autophagy or mitophagy promote oncogenesis[209], and indeed patients with FA are at a higher risk of developing different and often multiple cancer types[209]. Furthermore, these cancers are linked to the increased susceptibility of patients with FA to the DNA-damaging action of environmental carcinogens[209].

Population studies indicate that decreased ambient oxygen exposure with increasing altitude may reduce the risk of specific types of cancer, a hypothesis that is experimentally supported by the improved survival of cancer-prone p53 null mice housed in low ambient oxygen[210–212]. Moreover, selectively disrupting respiration by knocking out p53-regulated *SCO2*, a gene essential for cytochrome c oxidase assembly, resulted in extreme oxidative stress and a DNA damage response that could be prevented by decreasing ambient oxygen levels[213]. These basic experimental and epidemiological observations suggest there exists a complex gene x environment interaction (GxE) scenario involving a critical tumor suppressor gene and ambient oxygen without which life is not possible.

However, even though it is known that ROS can mediate DNA damage and promote transformation, the roles of oxidative stress and counterbalancing antioxidant responses in the progression of cellular transformation are complex. Harris et al.[214] demonstrated that antioxidants are required for cancer onset in at least three genetic mouse models of carcinogenesis: the development of mammary tumours in PyMT transgenic mice, sarcomas in LSL-$Kras^{G12D+/-}$;$Trp53^{fl/fl}$ Ad-Cre mice, and lymphomas in $Pten^{+/-}$ mice[214,215]. The failure of modulation of oxidative stress (i.e. interfering with GxE) as an anticancer strategy in these three models suggested that high ROS levels are harmful to premalignant cells. Altering the ‘E’ component of ROS via antioxidants illustrates the intricacy of the balance between oxidative stress and redox functions in oncogenesis and underscores the controversy over the use of antioxidants in cancer prevention.

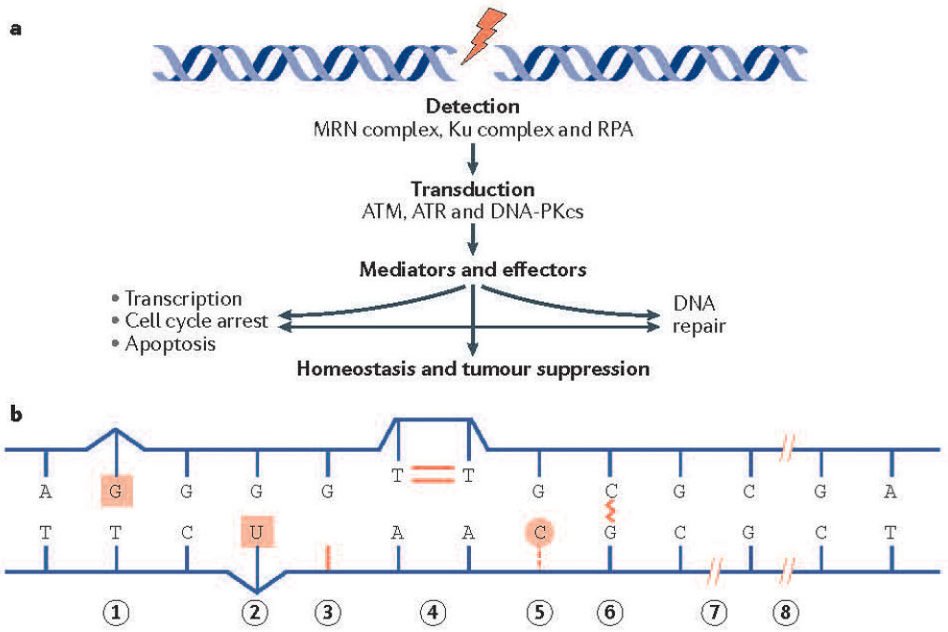

Figure 1. DNA repair pathways and cancer.

(A) The DNA damage response is activated by DNA damage sensors that include the MRE11–RAD50–NBS1 (MRN) complex and the Ku heterodimer, which detect DNA double-strand breaks. The replication protein A (RPA) heterotrimer engages exposed regions of single stranded DNA. These sensors recruit the transducing kinases ataxia telangiectasia mutated (ATM) (through the MRN complex), DNA-dependent protein kinase catalytic subunit (DNA-PKcs) (through the Ku heterodimer), and ataxia telangiectasia and Rad3-related protein (ATR) (through RPA), which in turn phosphorylate a broad spectrum of mediators and effectors. Ultimately the DNA damage response promotes survival at the cellular level and homeostasis and tumor suppression at the organismal level.

(B) Depicted are DNA lesions that can promote cancer development. Mismatch repair (MMR) corrects mismatched base pairs (lesion 1). Base excision repair [G] (BER) removes chemically damaged bases (lesion 2), repairs abasic sites (a location in DNA that has neither a purine nor a pyrimidine base due to DNA damage) (lesion 3) and repairs DNA nicks (where there is no phosphodiester bond between adjacent nucleotides of one strand) (lesion 7). Nucleotide excision repair (NER) is required for the removal of cyclobutane pyrimidine dimers (lesion 4) and 6–4 photoproducts (not shown) arising from exposure to ultraviolet (UV) light. NER and BER, along with alkyl transferases are responsible for removal of damaged bases and bulky adducts (lesion 5). The Fanconi anemia (FA) pathway removes intra-strand cross links (lesion 6). DNA double strand breaks can cause pathogenic DNA rearrangements, and are repaired by non-homologous end joining [G] (NHEJ) and homologous recombination (HR) pathways (lesion 8). The reader is directed to a comprehensive review[192].

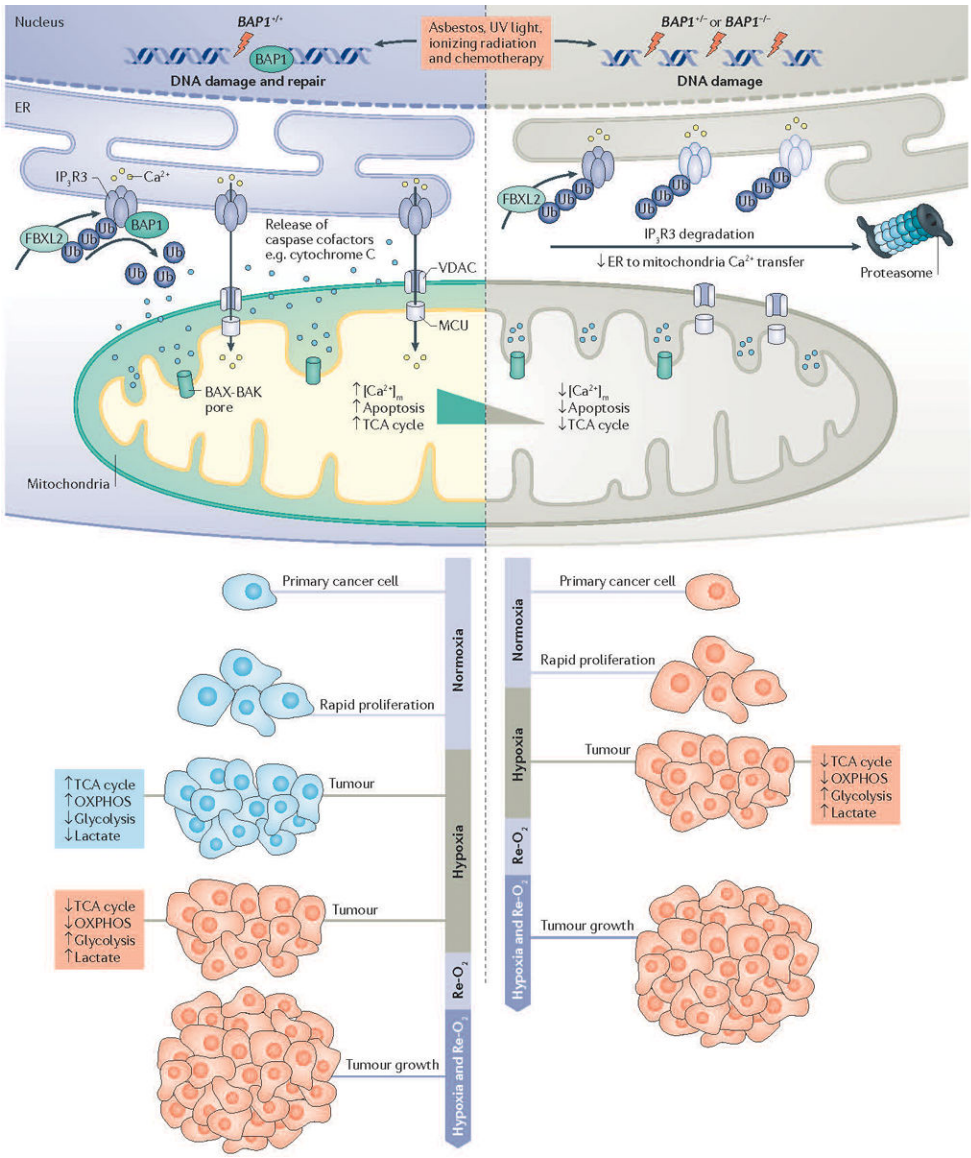

Figure 2. Mechanisms of BAP1 activity in cancer development.

The powerful tumor suppressor activity of BRCA1-associated protein 1 (BAP1) and its ability to regulate gene x environment interactions (GxE) in carcinogenesis are related to its dual role in the nucleus, where BAP1 contributes to DNA repair by modulating homologous recombination (HR), and in the cytoplasm where BAP1 regulates cell death and mitochondrial respiration[30]. In the cytoplasm, BAP1 localizes at the endoplasmic reticulum (ER) where it binds, deubiquitylates (following F-box and leucine-rich repeat protein 2 (FBXL2) ubiquitylation), and stabilizes type 3 inositol-1,4,5-trisphosphate receptor (IP_3R3), modulating calcium ion (Ca^{2+}) release from the ER into the cytosol and mitochondria, and thus promoting apoptosis[30]. In primary cells exposed to either asbestos, ionizing radiation (IR) or ultraviolet (UV) radiation, reduced levels of nuclear BAP1 impair DNA repair. At the same time, reduced cytoplasmic BAP1 levels impair apoptosis, increasing the fraction of cells that survive DNA damage and that over time may become malignant[30]. In addition,

mitochondria need Ca^{2+} for aerobic oxidative phosphorylation (OXPHOS). In response to tumor hypoxia, cancer cells need to adjust their metabolism from aerobic (blue) to glycolytic (red) in order to sustain growth and survival. Primary cells from *BAP1*$^{+/-}$ individuals have reduced mitochondrial OXPHOS and increased aerobic glycolysis and lactate production, even in the presence of oxygen, a phenomenon known as the 'Warburg effect'[56]. Therefore, the 'Warburg effect' in addition to being a hallmark of cancer cells is also found in normal cells from *BAP1*-mutant carriers, and contributes to the adaptation to metabolic stress during tumorigenesis[56]. *BAP1*$^{+/+}$, cells with *BAP1* wild-type; *BAP1*$^{+/-}$, cells with heterozygous *BAP1* mutations, containing about 50% of BAP1 protein levels compared to wild-type cells[30]. $[Ca^{2+}]_m$, mitochondrial calcium; MCU, mitochondrial calcium uniporter; Re-O_2 reoxygenation; TCA, tricarboxylic acid; Ub, ubiquitin; VDAC, voltage-dependent anion channel.

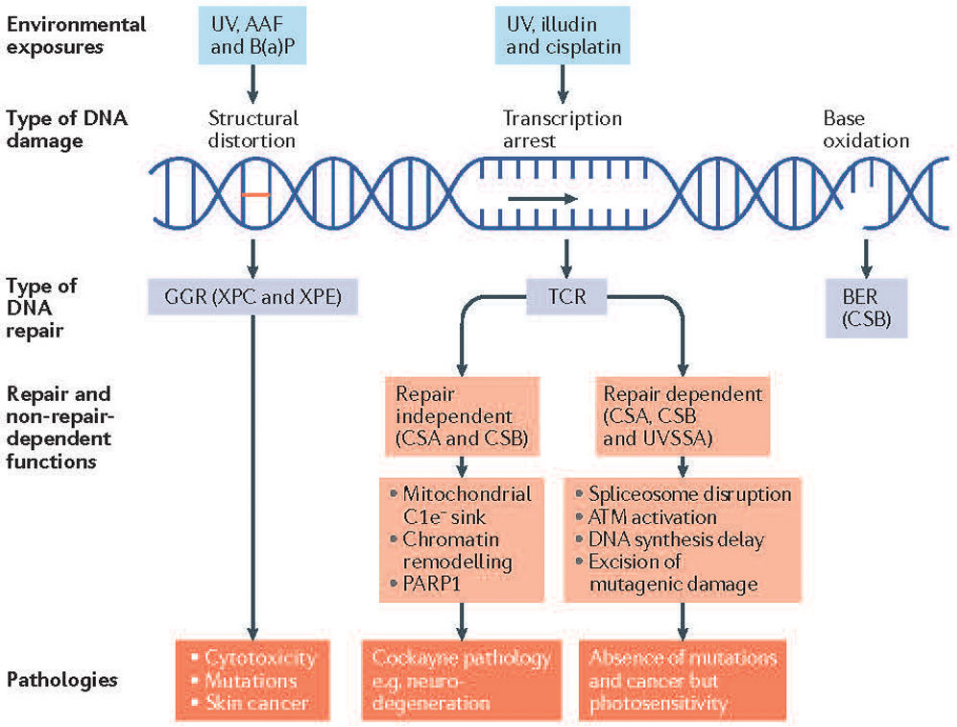

Figure 3. Xeroderma pigmentosum and Cockayne syndrome as examples of environmental impacts and genetics on DNA damage and repair.

Pathways activated by DNA damage depend on the nature of the damage, cell cycle stage, and the DNA damage response. The proteins in these pathways also have roles beyond DNA repair. DNA damage from exogenous agents that distort the DNA double helix creates a target for global genome repair (GGR) also known as GG-nucleotide excision repair (GG-NER). Examples include N-2-acetylaminofluorene (AAF) (a carcinogenic and mutagenic derivative of fluorene that forms adducts at the C8 position of guanine in DNA) and benzo[a]pyrene (B(a)P) (a polycyclic aromatic hydrocarbon that also forms DNA adducts). Xeroderma pigmentosum (XP), mutations in the damage recognition proteins xeroderma pigmentosum complementation group E (XPE) and XPC cause increased ultraviolet (UV)-specific mutations and cancer in exposed tissues, mainly skin. Agents such as the fungal toxin illudin and the chemotherapeutic agent cisplatin & its derivatives arrest transcription and provide sites for rapid repair of the transcribed strand (known as transcription coupled repair (TCR) or TCR-NER). Arrested transcription disrupts spliceosomes [G] and activates ataxia telangiectasia mutated (ATM) kinase that downregulates DNA synthesis to provide adequate time for repair thereby preventing mutagenesis. Cockayne syndrome-type A (CSA) & CSB proteins, but not UV-stimulated scaffold protein A (UVSSA), have roles in mitochondrial function, the repair of oxidative damage and chromatin remodeling among other downstream functions. CSB also functions as a sink for excess electrons released from complex 1 ($C1e^{-}$) of the mitochondria[76]. In Cockayne syndrome (CS) and ultraviolet sensitive syndrome (UVS), mutations in *CSA* or *CSB* and *UVSSA*, respectively cause repair-dependent pathologies such as photosensitivity but only mutations in *CSA* or *CSB* cause additional pathologies such as neurodegeneration, deafness, loss of subcutaneous fat,

developmental delay and short lifespans. BER, base excision repair; PARP1, poly(ADP-ribose) polymerase 1.

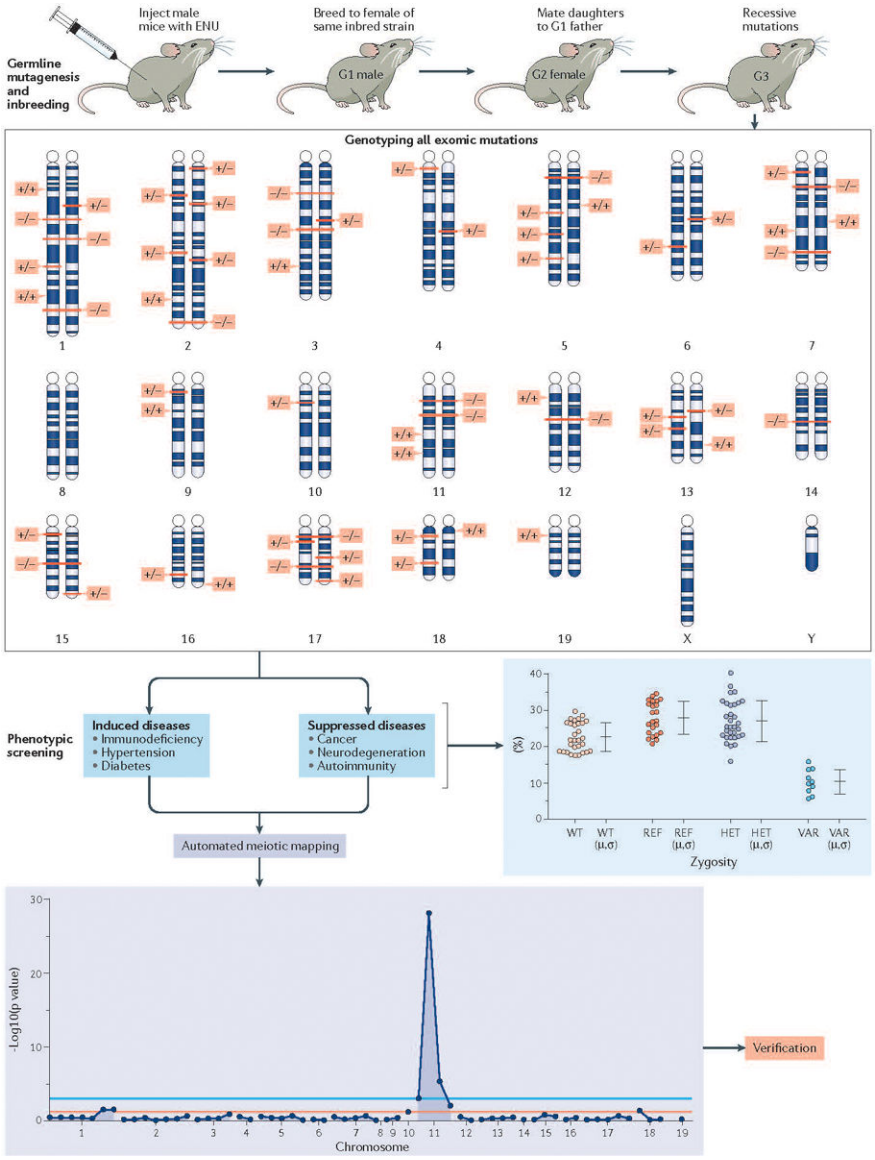

Figure 4. Using ENU mutagenesis to create and ameliorate disease in mice.

Male C57BL/6J mice are injected with three weekly doses of the highly potent mutagen N-ethyl-N-nitrosourea (also known as ENU). Mutations in spermatogonia are transmitted via sperm, which contain an average of 60 coding or splicing changes each (The number that cause coding or splicing changes averages 60 per spermatozoa). G1 male offspring are sequenced at the whole exome level to identify these mutations in the heterozygous state, and then bred to produce G2 daughters, all of which are backcrossed to their sire. In the resulting G3 generation, each mutation site can be a homozygous or heterozygous mutant allele, or homozygous reference allele. All mutation sites are genotyped in each of about 40 G3 mice prior to phenotypic screening, usually entailing quantitative (continuous variable) assays of biological function, performed using intact mice or cells derived from them. Irrespective of the phenotype (either induction of disease or suppression of disease), it can be mapped with high confidence, often occurring in multiple allelic forms over many

pedigrees. Statistical computation assigns causation of each phenotype to a specific mutation, and causation is verified by CRISPR–Cas9 targeting in a non-mutagenized animal. Forward genetic screens to identify the gene underlying a phenotype has already led to many discoveries in the realm of immunology. For example, defective lipopolysaccharide (LPS) signaling in C3H/HeJ and C57BL/10ScCr mice led to the identification of the Toll-like receptor 4 (TLR4) as the receptor for LPS[193], and the fatal X-linked lymphoproliferative disorder observed in the *scurfy* mouse led to the realization that the protein product of forkhead box protein 3 (*Foxp3*), scurfin, is essential for normal immune homeostasis[194].

Table 1:

Key features of some of the tumor predisposition syndromes and cancer syndromes

Syndrome	Gene(s)	Inheritance pattern	Key pathways implicated	Typical age of earliest clinical onset	Key malignant tumors	Lifetime risks for these tumors	Frequent benign manifestations	Founder mutations	Mutations also present in histologically similar, sporadic tumors	Evidence of GxE
BAP1,	*BAP1*	AD	DNA repair and mitochondrial regulated cell death	Adolescence	Mesothelioma, clear cell RCC, uveal melanoma	~100% cancer risk MM: 25% RCC: 15% UVM; 30%	MBAITs	In multiple populations	Frequent	Yes
Birt-Hogg-Dubé,	*FLCN*	AD	AKT-mTOR signaling and TFE3 transcriptional regulation	Adolescence	RCC (hybrid oncocytic or chromophobe type)	12–34% 7-fold elevated risk over unaffected controls	Fibrofolliculomas, lung cysts, spontaneous pneumothorax	No	Rare	Possible
Bloom,	*BLM*	AR	Homologous recombination	*in utero*	Multiple cancer types	~50% for one or more malignancy	Multiple non-cancer phenotypes, including growth retardation and photosensitivity	Ashkenazi Jews	Rare	Likely
Cockayne, 1934 (UV sensitive syndrome)	*CSA, CSB, UVSSA*	AR	TCR, base excision repair	First decade (not UVSSA)	No cancers reported (skin cancer in mouse models)	Not applicable	Developmental delay, aging, neurological disorders (not UVSSA)	No	Not applicable	Sun-light photosensitivity of skin
DICER1	*DICER1*	AD	microRNA biogenesis	Childhood	Pleuropulmonary blastoma (PPB), ovarian sertoli-leydig cell tumor (OSLCT), genitourinary and cerebral sarcomas	PPB <20%, OSLCT <10%, Genitourinary and cerebral sarcomas: <10%	Multinodular goiter, cystic nephroma	No	Frequent	Possible
Fanconi Anemia,	multiple	AR	FA pathway	Childhood	Myeloid leukemia, squamous cell carcinoma, hepatocellular carcinoma and others	To age 48: 10% Leukemia, 29% for Solid tumors,	None	Ashkenazi Jews	Frequent	Yes
Li-Fraumeni,	*TP53*	AD	p53-mediated DNA damage repair	Infancy through to seventh decade	Most cancer types; breast, brain, sarcomas, adrenocortical	Males: 75% Females: 93–100%	None	Brazil	Frequent in carcinomas; rare in sarcomas.	Yes
Lynch	*MLH1, MSH2, MSH6, PMS2*	AD (AR results in CMMRD)	MMR genes inactivation	Young adults	Colon Cancer, stomach cancer (high prevalence in Asia) and other cancer types.	Highly variable	Colon adenomas (precursors of carcinomas)	In multiple populations	Occasional	Yes
Tuberous Sclerosis Complex	*TSC1, TSC2*	AD	mTORC1	Childhood, but can be missed until adulthood	RCC, Lymphangioleiomyomatosis (LAM)	RCC: 5% LAM: 40% of women	Facial angiofibroma, cardiac rhabdomyoma, renal angiomyolipoma, subependymal giant cell astrocytoma, and others	No	Yes, in sporadic angiomyolipoma and LAM	Yes, facial angiofibromas and sun exposure
Werner	*WRN*	AR	DNA replication, recombination and repair; transcription	Adolescence	Thyroid carcinoma, atypical melanoma, meningioma, bone or soft tissue sarcomas	10 to 60-fold elevated risk over population controls	Bilateral cataracts, scleroderma-like skin changes, premature graying and/or loss of hair	Japan, India, Sardinia, Syria	Occasional	Likely
Xeroderma pigmentosa	XPA,XPB,XPC,XPD,XPE,XPV	AR	TCR-NER	First decade or later	Skin cancer: non-melanoma and melanoma	Melanoma 2000x. Non-melanoma 10,000x	Photosensitivity, neurodegeneration, hair loss	Guatemala, Tunisia, Egypt, and others	No	Yes

AD, autosomal dominant; AR, autosomal recessive; CMMRD, constitutional mismatch repair defect (caused by biallelic pathogenic variants in mismatch repair genes); CS, Cockayne syndrome type; FA, Fanconi anemia; *FLCN*, folliculin; GxE, gene x environment; MBAITs, melanocytic BAP1-associated intradermal tumours; *MLH1*, mutL homologue 1; MMR, mismatch repair; MSH, mutS homologue; mTORC1, mTOR complex 1; NER, nucleotide excision repair; *PMS2*, postmeiotic segregation increased 2; RCC, renal cell carcinoma; TCR, transcription coupled repair; TFE3; transcription factor E3; UVSSA, UV-stimulated scaffold protein A; XP, xeroderma pigmentosum complementation.