CMLS, Cell. Mol. Life Sci. 57 (2000) 589–603
1420-682X/00/040589-15 $ 1.50 + 0.20/0

CMLS Cellular and Molecular Life Sciences

Review

The inherited susceptibility to cancer

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Received 6 October 1999; received after revision 29 November 1999; accepted 12 December 1999

Abstract. The study of inherited cancer syndromes has led to the identification of over 25 genes directly involved in tumorigenesis. These genes have functions as diverse as signal transduction, cell cycle control, cell-to-cell adhesion, control of apoptosis, DNA repair and the maintenance of genome stability. Most cancer syndromes have a dominant pattern of inheritance, due to germline loss-of-function mutation of a tumour suppressor gene. All the recessively inherited genes have been implicated in the maintenance of genome stability. This review summarises our current understanding of the functions of the major cancer susceptibility genes.

Key words. Cancer; familial; inherited; predisposition; susceptibility; gene.

Introduction

The normal cellular processes of proliferation, migration, differentiation and programmed death provide the tools by which malignancies develop. The diversity and complexity of these processes dictate that the genes which predispose to inherited cancer will be numerous and varied in function (table 1). This variety, combined with the propensity of many genes to encode proteins with multiple functions, defies simple classification of cancer susceptibility genes. Here they will be divided into two broad categories: (i) genes involved in cell communication, proliferation and survival, and (ii) genes required for genome stability and DNA repair. Polymorphisms in genes that mediate the metabolism and detoxification of environmental carcinogens, such as the acetyltransferase genes *NAT1* and *NAT2*, the cytochrome p450 genes, and the glutathione transferase gene *GSTM1*, provide a third category of cancer susceptibility genes. This category of genes is reviewed elsewhere [1].

The implicit limitation on inherited disease susceptibility genes is that heterozygous germline mutations cannot be embryonically lethal. Consequently, gain-of-function germline mutations are rare in the genes encoding the fundamental proliferative and developmental pathways. Instead, the majority of inherited cancer syndromes have a dominant mode of inheritance caused by a loss-of-function mutation in a single allele of a tumour suppressor gene [2]; somatic inactivation of the second allele is then required for the phenotypic changes associated with cancer progression [3]. The few known exceptions are activating missense mutations in the *KIT*, *RET* and *MET* receptor tyrosine kinase genes, dominant-negative mutations in the DNA-binding domain of *P53* in Li-Fraumeni syndrome, and missense mutations in *CDK4* which abrogate $p16^{INK4a}$ binding and predispose to malignant melanoma. Notably, the few genes responsible for recessively inherited cancer susceptibility are not directly involved in the pathways associated with tumorigenesis, but instead encode proteins implicated in genome stability and DNA repair.

Cell communication, proliferation and survival

RB1: familial retinoblastoma

Germline mutation of the *RB1* gene predisposes to early-onset retinoblastoma, and an elevated risk of osteosarcoma. RB1 is a multifunctional protein, with roles in regulating the mitotic cell cycle, apoptosis and differentiation [reviewed in ref. 4]. It is, however, its role as a negative regulator of the mitotic cell cycle that is likely to dominate its involvement in tumorigenesis.

Mitogenic stimulation of the cell leads to the synthesis of members of the cyclin families of cell cycle proteins. Cyclins bind and activate different cyclin-dependent kinases (CDKs) which in turn phosphorylate RB1. RB1 in its unphosphorylated state inhibits progression through the late G1 phase of the cell cycle by blocking the activity of E2F transcription family members and consequently repressing transcription of the diverse E2F target genes. However, progressive phosphorylation in mid to late G1 phase by one or more of the cyclin-activated CDKs uncouples RB1 from the E2F transcription factors, enabling expression of their target genes and entry of the cell into S phase [5].

Table 1. Summary of genes responsible for inherited cancer predisposition, their chromosomal location, the syndromes they cause and the functions of the gene products (mode of inheritance is shown in italics).

Gene	Syndrome	Location	Principal function	Principal malignancies
RB1	familial retinoblastoma; *dominant*	13q14	transcriptional/ cell cycle regulator	retinoblastoma
P16^{INK4a}	familial melanoma; *dominant*	9p21	CDK inhibitor	melanoma
CDK4	familial melanoma; *dominant*	12q13	CDK	melanoma
P53	Li-Fraumeni; *dominant*	17p13.1	transcription factor	sarcomas, breast cancer
APC	familial adenomatous polyposis; *dominant*	5q21	growth factor signalling	colorectal cancer
CDH1	hereditary diffuse gastric cancer; *dominant*	16q22.1	cell-to-cell adhesion	diffuse gastric cancer
LKB1	Peutz-Jeghers; *dominant*	19p13.3	serine threonine kinase	gastrointestinal cancer
PTEN	Cowden syndrome; juvenile polyposis coli; *dominant*	10q23.3	phosphatase, cytoskeletal protein?	breast cancer, gastrointestinal cancer
SMAD4	juvenile polyposis coli; *dominant*	18q21.2	growth factor signalling	gastrointestinal cancer
MEN1	multiple endocrine neoplasia type 1; *dominant*	11q13	transcription co-factor	endocrine
RET	multiple endocrine neoplasia type 2; *dominant*	10q11.2	receptor tyrosine kinase	endocrine
MET	Hereditary papillary renal cancer; *dominant*	7q31	receptor tyrosine kinase	papillary renal cancer
KIT	familial gastrointestinal stromal tumours; *dominant*	4q12	receptor tyrosine kinase	gastrointestinal cancer (stromal)
PTCH	basal cell nevus syndrome; *dominant*	9q22.3	membrane receptor	basal cell (skin)
NF1	neurofibromatosis type 1; *dominant*	17q11.2	GTPase-activating protein	neurofibrosarcomas
NF2	neurofibromatosis type 2; *dominant*	22q12.2	cytoskeletal protein?	central nervous system tumours
VHL	von Hippel-Lindau *dominant*	3p25	protein maturation? RNA elongation?	renal clear cell carcinomas, pheochromocytomas
WT1	Wilms tumour; *dominant*	11p13	transcription factor	nephroblastoma
BLM	Bloom syndrome; *recessive*	15q26.1	dsDNA repair?	leukaemia, lymphoma
FANCA; *FANCC*; others	Fanconi anaemia; *recessive*	16q24.3; 9q22.3; ?	dsDNA repair?	leukaemia
XPB; *XPD* others	xeroderma pigmentosum; *recessive*	2q21; 19q13; ?	helicases, nucleotide excision repair	basal cell and squamous cell carcinomas
ATM	ataxia telangiectasia; *recessive*	11q22.3	serine-threonine protein kinase	lymphoma, leukaemia
NBS1	Nijmegen breakage syndrome; *recessive*	8q21	transcription factor? dsDNA repair?	lymphoma
BRCA1	familial breast/ovarian cancer; *dominant*	17q21	transcription factor? dsDNA repair	breast, ovarian cancer
BRCA2	familial breast/ovarian cancer; *dominant*	13q12	transcription factor? dsDNA repair	breast, ovarian cancer
MLH1; *MSH2* *PMS1*; *PMS2*; *MSH6*	hereditary non-polyposis colorectal cancer; *dominant*	3p21; 2p16; 2q32; 7p22; 2p16	DNA mismatch repair	colorectal, endometrial cancer

CDK, cyclin-dependent kinase.

P16 ^{INK4a} and *CDK4*: familial melanoma

Greater than 40% of melanoma-prone kindreds have mutations in the *$P16^{INK4a}$* (also known as CDKN2) gene on chromosome 9p21 [6]. Germline mutation of *$P16^{INK4a}$* increases the risk of melanoma by a factor of 75 and pancreatic cancer by a factor of over 10. A range of other cancers, including tumours of the cervix, bladder and breast, gliomas and certain haematological malignancies also occur in rare families [7]. Dysplastic nevi are also often associated with familial melanoma.

$p16^{INK4a}$ is a member of a group of CDK inhibitors that specifically bind to and inactivate cyclin-CDK complexes. Mammalian CDK inhibitors also include $p15^{INK4b}$, $p18^{INK4c}$, $p19^{INK4d}$, $p21^{CIP1}$, $p27^{KIP1}$ and $p57^{KIP2}$. $P16^{INK4a}$ itself binds to CDK4 and CDK6, preventing their association with cyclin D [8]. Inhibition of CDK4/6 binding to cyclin D blocks RB1 phosphorylation which in turn decreases the expression of the E2F-dependent genes that control the G1–S transition of the cell cycle.

$p16^{INK4a}$ mutations are not the only germline mutations associated with familial melanoma. Rare melanoma-prone families have been identified with wild-type *$p16^{INK4a}$* but missense mutations in *CDK4*. These missense mutations abrogate the interaction between $p16^{INK4a}$ and CDK4 [6, 9, 10] causing a phenotype comparable to the effect of loss of function *$P16^{INK4a}$* mutations.

The *$P16^{INK4a}$* gene partially overlaps an open reading frame known as *$P19^{ARF}$*. Although $p19^{ARF}$ has been implicated in tumorigenesis [11], the germline mutations found in familial melanoma probably do not impair $p19^{ARF}$ function [12].

$p16^{INK4a}$ is expressed at low to undetectable levels in developing embryos, and is not required for normal development [13]. As well as regulating the cell cycle, $p16^{INK4a}$ may also play a role in limiting the lifespan of proliferative cells [reviewed in ref. 14], a process known as replicative senescence. The appearance of the senescent phenotype is correlated with the production of $p16^{INK4a}$. Mutation or deletion of *$P16^{INK4a}$* has been implicated in the immortalisation process of cell lines. Embryo fibroblasts from mice that are nullizygous for *$P16^{INK4a}$* do not senesce, whereas wild-type cells undergo senescense after 10–12 doublings accompanied by a sharp rise in $p16^{INK4a}$ levels [15, 16]. The ectopic expression of $p16^{INK4a}$ can induce senescense in relatively young fibroblasts [17].

P53: Li-Fraumeni syndrome

Li-Fraumeni syndrome is characterised by susceptibility to a broad range of cancers including rhabdomyosarcoma, osteogenic sarcoma, breast cancer, brain cancer, leukaemia and adrenal cortical carcinoma [7]. Genetically it is defined by germline mutation of the inhibitor of the mitotic cell cycle and promoter of apoptosis, *P53*.

Intracellular levels of p53 are controlled by competing systems that either stabilise or destabilise p53 in response to DNA damage or cytokine stimulation. Key regulators of p53 stability are the proteins mdm2 and $p19^{ARF}$ [reviewed in ref. 18]. mdm2 masks the p53 activation domain [19] and is able to promote the degradation of p53 [20, 21]. In response to DNA damage, p53 is phosphorylated by protein kinases including ATM and DNA-dependent protein kinase. These phosphorylation events are likely to prevent mdm2-dependent degradation of p53. In contrast to mdm2, $p19^{ARF}$ stabilises and activates p53, probably by its ability to bind mdm2 and/or p53 itself. $p19^{ARF}$ activity is stimulated by overexpression of oncogenes such as c-*myc*, *E2F1* and *E1A* [5].

Much of the activity of p53 can be ascribed to its ability to enhance transcription by specific interaction with the DNA sequence 5′-PuPuPuC(A/T)(T/A)GPyPyPy-3′ [22]. In response to DNA damage or inappropriate activation of oncogenes, p53 is stabilised and initiates cell cycle arrest at either the G1–S or G2–M transitions. The G1–S arrest is in part mediated by transcriptional up-regulation of the cyclin-dependent kinase inhibitor $p21^{CIP1}$ by p53 [23]. G2–M arrest (which prevents improper chromosome segregation) is mediated by p53-induced transcriptional activation of the cell cycle checkpoint gene *GADD45* [24] and *14.3.3σ* a human homologue of the yeast checkpoint genes *RAD24* and *RAD25* [25].

The mechanism by which p53 promotes apoptosis has been less clearly defined but is likely to involve transcriptional activation of the mitochondrial-associated pro-apoptotic protein Bax [26] and a group of proteins implicated in the cell response to oxidative stress known as PIGs (p53-induced genes) [27]. P53 can also enhance apoptosis by transiently increasing export of a member of the tumour necrosis receptor family, Fas, from the Golgi complex to the cell surface [28]. The Fas-related apoptotic pathway is rapid and independent of new RNA or protein synthesis [28].

Germline missense mutations in the core DNA-binding domain of *P53* account for about three-quarters of the Li-Fraumeni mutations [7, 29]. Families with missense mutations in this domain have a more highly penetrant phenotype than families with protein-truncating mutations. In particular, the former have a younger age of onset and a higher incidence of breast cancers and brain tumours [29]. Because p53 functions as a tetramer, the missense mutations would have a dominant-negative effect; therefore, somatic inactivation of the wild-type allele would not be essential for tumour progression. Indeed, in one study of Li-Fraumeni families, loss of heterozygosity (LOH) was only observed in about one-

third of the tumours with missense mutations in the DNA-binding domain, but in all tumours with either truncating mutations or mutations outside the DNA-binding domain [29].

APC: familial adenomatous polyposis

Germline mutation of the *APC* gene is responsible for familial adenomatous polyposis (FAP). FAP is characterised by the development of large numbers of pre-malignant adenomatous colorectal polyps. Unless the colon is surgically removed, FAP patients have a near 100% risk of developing colon adenocarcinoma. Other associated malignancies include duodenal carcinoma, thyroid cancer, gastric cancer and tumours of the central nervous system, principally medulloblastomas [30].

APC forms part of a complex including glycogen synthase kinase-3β (GSK-3β) and axin [31] that regulates signalling through the *Wnt* pathway. In the absence of signalling, APC and the multi-functional protein β-catenin are phosphorylated by GSK-3β [32]. Phosphorylated β-catenin is ubiquinated and degraded in the proteosomes [33, 34]. *Wnt* signalling inhibits GSK-3β activity, leading to an increase in free β-catenin. β-Catenin binds to the LEF/TCF transcription factors and migrates to the nucleus where it acts as a transcriptional co-activator of genes such as c-*myc*, cyclin D1 [35], and components of the AP-1 transcription complex (c-*jun* and *fra-1*) [36]. β-Catenin up-regulation is also correlated with changes in the expression of genes involved in cell adhesion and motility. These changes include increased expression of fibronectin [37] and urokinase-type plasminogen activator receptor [36] and decreased expression of E-cadherin [38, 39] and the tight junction protein ZO-1 [36].

β-Catenin can also regulate cell adhesion and motility by virtue of its ability to bind the cytoplasmic domain of the cell-to-cell adhesion protein E-cadherin. This interaction is required for adhesion at the adherens junctions on the basolateral surface of the cell. APC is able to compete with E-cadherin for binding to β-catenin [40, 41], and therefore may also play a direct role in the regulation of cell adhesion.

In addition to its role modulating the activity of β-catenin, APC is believed to regulate the rate of intestinal crypt production by controlling crypt fission [42]. Increased crypt fission would enhance polyp formation in the intestinal tracts of germline *APC* mutation carriers. Finally, it has also been suggested that APC may play a role in the response of the cell to DNA damage [43].

Classical FAP is caused by high-penetrance *APC* mutations that generally result in protein truncation. However, attenuated phenotypes have been attributed to mutation of the 5′ and 3′ regulatory regions of *APC* [44–46]. Recently, a specific missense germline mutation (I1307K) in the *APC* gene has been described which leads to an increased risk of somatic mutation (particularly insertions) by creating a hypermutatable tract of A residues [47]. The I1307K mutation provides an example of a high-prevalence, low-penetrance cancer susceptibility mutation. It is present in $\sim$7% of unselected Ashkenazi Jews and increases the risk of colorectal adenoma or carcinoma by a modest 1.5- to 1.7-fold [48]. A second substitution mutation (E1317Q) in *APC* has also been associated with low- and variable-penetrance colorectal adenomas and carcinomas [49].

CDH1: hereditary diffuse gastric cancer

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer syndrome caused by germline mutation of the gene for the cell-to-cell adhesion protein E-cadherin (*CDH1*) [50]. Tumours in this syndrome are predominantly histologically diffuse, poorly differentiated gastric cancers, but an elevated risk of colorectal and breast cancer may exist [51–53]. Germline *CDH1* mutation is not associated with the intestinal form of gastric cancer [54].

E-cadherin is a homophilic transmembrane protein localised to the adherens junction on the basolateral surface of the cell [55]. The cytoplasmic domain forms a complex with proteins of the catenin family, which mediate an interaction between E-cadherin and the actin cytoskeleton. E-cadherin therefore effectively forms a continuum between the cytoskeletons of adjacent cells.

In vitro and in vivo, E-cadherin loss is associated with the acquisition of an invasive phenotype [56–58]. In a mouse model of pancreatic β-cell tumorigenesis, progression from well-differentiated adenoma to invasive carcinoma coincided with E-cadherin down-regulation [59]. E-cadherin loss may also play a role in tumour initiation by disrupting signalling through the *Wnt* pathway [60]. In vitro, cadherin expression at the cell surface has been demonstrated to sequester β-catenin to the adherens junctions leading to an inhibition of LEF-1-directed transcription [61]. However, loss of E-cadherin expression may not be sufficient to constitutively activate signalling through the *Wnt* pathway [62].

LKB1: Peutz-Jeghers syndrome

Germline mutations in *LKB1* underlie familial Peutz-Jeghers syndrome (PJS). PJS is characterised by intestinal hamartomatous polyps, pigmented spots and an elevated risk of various neoplasms including gastrointestinal, gynaecological and breast cancers [63]. Although *LKB1* is the major locus for PJS, this syndrome is genetically heterogeneous [64].

LKB1 is ubiquitously expressed, with highest expression in the testes [65]. The gene is composed of ten exons spanning 23 kb and encodes a serine/threonine kinase of unknown specificity [66, 67]. Somatic mutations in *LKB1* have been reported in diverse sporadic tumour types, but at a very low frequency [68].

PTEN: Cowden syndrome; juvenile polyposis coli

Cowden disease is characterised by hamartomas (disorganised cell masses) of multiple organs, including skin, breast, thyroid and the gastrointestinal tract. Lipomas, fibroadenomas of the breast, cerebellar gangliocytomatosis and haemangiomas are also common [7]. In addition to these benign tumours, breast cancers develop in 30–50% of affected woman. An increased risk of other cancer types, in particular thyroid carcinoma, is also likely.

Juvenile polyposis coli (JPC) is a variant of Cowden disease which is characterised by the development of hamartomatous polyps throughout the digestive tract and a predisposition to cancer of the gastrointestinal tract and possibly the pancreas. These polyps, unlike those in FAP and PJS, are distinguished by an overgrowth of stromal cells, but contain a normal epithelial component.

Germline mutation of the tumour suppressor gene *PTEN* leads to both Cowden disease and JPC. The phenotypic differences observed between the two may reflect the location of the mutations within the *PTEN* gene or the influence of different genetic backgrounds [69]. PTEN contains a dual-specificity phosphatase domain and a region of homology to the cytoskeletal proteins, tensin and auxillin. It is able to dephosphorylate both phosphotyrosine and phosphoserine/threonine-containing substrates in vitro [70]. Loss of PTEN results in decreased sensitivity to cell death in response to diverse apoptotic stimuli. PTEN dephosphorylates phosphatidylinositol (3,4,5) triphosphate (PIT), a direct product of phosphatidylinositol 3 kinase activity [71]. PIT participates in the activation of the serine/threonine kinase Akt. Akt is a regulator of a cell survival pathway that mediates the anti-apoptotic signals from several growth factors including insulin-like growth factor (IGF)-1 [72] and interleukin (IL)-2 [73]. Elevated Akt signalling also protects cells from apoptosis induced by diverse stimuli including matrix detachment [74] and c-*myc* overexpression [75]. In addition to its role as a negative regulator of the Akt cell survival pathway [76–78], PTEN is able to inhibit cell migration, integrin-mediated cell spreading and focal adhesion through its ability to directly dephosphorylate focal adhesion kinase [79].

SMAD4: juvenile polyposis coli

In addition to germline mutations in the *PTEN* gene, *SMAD4* germline mutations are also found in families affected by JPC [80].

SMAD4 is a member of the *SMAD* family of genes that encode cytoplasmic mediators of the transforming growth factor (TGF)-β signalling pathway. TGF-β inhibits growth of many tissues, including the colonic epithelium, and TGF-β resistance has been associated with colorectal cancer [81]. Binding of TGF-β or related ligands to their serine/threonine kinase receptors results in phosphorylation of SMAD2 and/or SMAD3, which then form complexes with SMAD4. These complexes migrate to the nucleus where they bind both specific DNA sequences [82] and transcription factors such as the Jun family of AP-1 transcription factors [83]. The target genes of the TGF-β pathway include the CDK inhibitors $P21^{CIP1}$ and $P15^{INK4b}$ [84, 85] and plasminogen activator inhibitor-1 [86].

MEN1: multiple endocrine neoplasia type 1

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disease characterised by peptic ulcers and endocrine abnormalities, in particular hyperparathyroidism. Associated malignant neoplasms include tumours of the parathyroids, pancreatic islets and anterior pituitary. In addition, adrenocortical carcinomas, carcinoid tumours and schwannomas are occasionally observed. MEN1 is caused by mutation of the tumour suppressor gene *MEN1* [87, 88]. These mutations are predominantly nonsense or frameshift, and therefore inactivating.

MEN1 encodes a nuclear protein known as menin. Menin interacts with a member of the AP-1 family of transcription factors, JunD, and represses JunD-activated transcription in vitro [89]. The identities of the specific transcription targets of the menin-JunD complex are not yet known.

RET: multiple endocrine neoplasia type 2/familial medullary thyroid carcinoma

Multiple endocrine neoplasia type 2 (MEN2) is characterised clinically by the occurrence of medullary thyroid carcinoma and variable expression of pheochromocytomas, hyperparathyroidism, ganglioneuromas and mucosal neuromas. Medullary thyroid carcinoma occurs in isolation in familial medullary thyroid carcinoma (FMTC). Both MEN2 and FMTC are caused by germline missense mutation of the receptor tyrosine kinase gene *RET* [90]. Hirschsprung disease, which is defined by the absence of intrinsic ganglion cells of the gastrointestinal tract, is a third variant resulting from *RET* mutation. Correlations have been reported be-

tween the specific mutations in *RET* and the clinical phenotype [91–93]. RET is the receptor for glial cell line-derived neurotrophic factor (GCNF).

MET: hereditary papillary renal carcinoma

Hereditary papillary renal carcinoma (HPRC) is characterised by a predisposition to multiple, bilateral papillary renal tumours. Germline missense mutations have been identified in the tyrosine kinase domain of the receptor tyrosine kinase gene *MET* in families with HPRC [94, 95]. Equivalent mutations activate both the *RET* and *KIT* oncogenes [90, 96].

MET binds hepatocyte growth factor/scatter factor (HGF/SF) with high affinity [97]. MET and HGF/SF are expressed in a diverse range of tissues, predominantly in cells of epithelial and mesenchymal origin, respectively [98]. Signalling from this growth factor/receptor complex promotes proliferation, cell motility and extracellular matrix invasion [99]. Mutations in *MET* induce metastasis in model systems [100]. These changes are associated with increased expression of ERK1/2, adding to evidence that MET acts, at least in part, through the ras-raf-MEK-ERK signalling pathway [100].

KIT: familial gastrointestinal stromal tumours

Gastrointestinal stromal tumours are the most common mesenchymal tumour of the human gastrointestinal tract. A germline gain-of-function mutation has been identified in the KIT receptor tyrosine kinase in a family with a history of this tumour type over four generations [101]. Activating *KIT* mutations are also found in sporadic gastrointestinal stromal tumours.

PTCH: basal cell nevus syndrome

Germline mutation of the *PTCH* gene is responsible for basal cell nevus syndrome, which is characterised by multiple basal cell carcinomas in 90% of mutation carriers. Occasional medulloblastomas, ovarian carcinomas and fibrosarcomas are also observed. Non-malignant features can include congenital malformations and cysts and fibromas in diverse tissues [7].

PTCH is the cell surface receptor for sonic hedgehog (Shh), a signalling molecule important in patterning processes during development [reviewed in ref. 102]. PTCH is part of a multi-component transmembrane complex that includes the G protein-coupled receptor-like molecule Smoothened (SMO). Upon binding of Shh to PTCH, the normal inhibitory effect of PTCH on SMO is removed, allowing SMO to transduce the Shh signal. In *Drosophila*, one of the targets of this signalling pathway is *wingless*. The human homologue of *wingless*, *Wnt*, initiates a signalling pathway implicated in a number of epithelial cancers. However, it is not yet clear why mutation of *PTCH*, which is expressed in a wide range of tissues, leads predominantly to basal cell carcinomas.

NF1: neurofibromatosis type 1

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder whose clinical features include neurofibromas, café-au-lait spots, optic glioma and iris hamartomas. Up to 15% of affected individuals develop neoplasms of neural crest origin, in particular neurofibrosarcomas. Abnormalities in Schwann cells are thought to be responsible for both the neurofibromas and neurofibrosarcomas [103]. The risk for other cancers, including leukaemia and Wilms tumour, is elevated [7].

NF1 is caused by germline mutations in the 60-exon gene *NF1* [104, 105]. A central domain in the *NF1* gene product, neurofibromin, is the only region to which a clear function has been ascribed due to its strong homology with ras-specific GTPase-activating proteins (GAPs) [106]. ras is a membrane-associated protein which can bind GTP and catalyse its hydrolysis to GDP [107]. Like other GTP-binding proteins, ras is active in the GTP-bound state and inactive in the GDP-bound state. The neurofibromin GAP domain can increase the slow intrinsic GTPase activity of ras by up to 10^5-fold [105]. Thus, GAP activity is a negative regulator of ras. Consequently, inactivating mutations in *NF1* cause elevated levels of activated ras and its downstream signals [108]. Similarly, activating mutations in ras itself decrease its intrinsic GTPase activity and render it resistant to GAP activity [109].

ras signals through pathways including the mitogen-activated protein (MAP) kinase cascade [110]. Following extracellular stimulation of the upstream receptor tyrosine kinases, ras binds and activates the serine/threonine kinase raf1, which in turn leads to the sequential activation of the dual-specificity kinase MEK1 and the ERK kinases [111]. The ERK kinases phosphorylate a variety of targets including transcription factors such as Elk-1 which are involved in the control of cell growth [112].

NF2: neurofibromatosis type 2

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder with clinical signs which include hearing loss, café-au-lait spots, cataracts, muscle weakness and neurofibromas [7]. The majority of these signs are attributable to malignant gliomas, vestibular schwannomas, meningiomas and spinal cord schwannomas.

Truncating mutations in the responsible gene, *NF2*, [113, 114] tend to cause a more severe disease with earlier onset than missense mutations and mutations in promoter elements [115, 116]. The NF2 protein, merlin, has structural homology to a family of proteins that link the actin cytoskeleton to membrane glycoproteins [113, 114], and is expressed in several different cell types including Schwann cells, meningeal cells and neurons. It is a phosphoprotein that is localised to cortical actin structures and enriched in dynamic regions of the membrane such as membrane ruffles [117]. The mechanism by which merlin loss leads to tumorigenesis is not yet clear. However, the observation that the level of merlin increases in cell lines under conditions of confluency and serum starvation suggests that it may be involved in regulating the response of the cell to negative growth signals from the external environment [118].

VHL: von Hippel-Lindau disease

Individuals affected by von Hippel-Lindau disease (VHL) develop a variety of tumours including renal clear-cell carcinomas, pheochromocytomas and vascular tumours of the central nervous system and retina [119]. VHL is caused by germline mutation of the tumour suppressor gene *VHL*. Mutant alleles can be separated on the basis of their tendency to cause pheochromocytomas or renal cell carcinomas [119].

pVHL has been proposed to participate in the down-regulation of transcriptional elongation by blocking the assembly of the tripartite elongation complex elongin [120]. VHL-associated tumours are typically hypervascular [121]. Cells lacking pVHL overproduce hypoxia-inducible mRNAs such as vascular endothelial growth factor (*VEGF*) mRNA [122] under normoxic conditions. This effect appears to be mediated at the level of mRNA stability rather than transcription elongation. pVHL has also been reported to control cell cycle progression through regulation of the steady-state levels of the CDK inhibitor $p27^{KIP1}$ [123].

Recently, pVHL has been shown to interact with fibronectin (directly or indirectly), and intact pVHL is required for assembly of the extracellular fibronectin matrix [124]. How VHL is involved in matrix assembly has not yet been elucidated; however, VHL-deficient cells are less able to eliminate misprocessed proteins such as those arising from impaired glycosylation [125]. This effect may be mediated by CUL2, a member of the cullin protein family, which binds to the VHL-elongin complex [126, 127]. Cullin proteins are believed to target certain cellular proteins for ubiquination and degradation [121]. Therefore, loss of pVHL may lead to the disruption of the extracellular matrix secondary to the accumulation of misfolded fibronectin.

WT1: Wilms tumour

Germline mutation of the *WT1* gene leads to predisposition to the childhood nephroblastoma known as Wilms tumour. It sometimes occurs in association with aniridia, genitourinary malformations and mental retardation (termed WAGR).

WT1, which plays an important role in kidney development and differentiation, is expressed in the developing kidney, developing genitourinary tract and undifferentiated haemopoietic cells [128]. Overexpression of *WT1* has also been reported in sporadic solid tumours and leukaemias [129], suggesting a general oncogenic role.

WT1 is a zinc-finger transcription factor that represses the transcription of genes including *IGF-II*, IGF-I receptor (*IGF-IR*) [130, 131] and the paired-box transcription factor *PAX2* [132]. It has also been reported to activate transcription of the CDK inhibitor $P21^{CIP1}$ and the differentiation marker *syndecan-1* [133]. WT1 can also bind RNA, including exon 2 of the *IGF-II* mRNA [134] and may therefore also regulate gene expression at the post-transcriptional level.

Genome stability and DNA repair

BLM: Bloom syndrome

Germline mutation of the *BLM* gene is responsible for Bloom syndrome, a rare autosomal recessive disorder characterised by growth deficiency, immunodeficiency, genomic instability and the predisposition to a wide range of cancers. The genomic instability is observed as excessive chromosome breakage and a dramatically elevated rate of sister chromatid exchange in somatic cells. Acute leukaemia and lymphoid neoplasms are the predominant cancers before the age of 25 years; cancers of the tongue, larynx, lung, oesophagus, colon, skin, breast and cervix have also been described in Bloom syndrome families [7]. BLM protein, which is localised to the nucleus, encodes a protein with homology to the *Escherichia coli* recQ subfamily of 3′–5′ DNA helicases [135] and the fission yeast protein RAD12+. RAD12+ is implicated in both chromosome segregation and G2 checkpoint regulation [136]. Another homologue of the *E. coli* recQ helicases is responsible for Werner syndrome, a rare autosomal recessive disorder causing premature ageing and cancer predisposition [137].

Fanconi anaemia complementation groups

Fanconi anaemia is an autosomal recessive disease with varied clinical symptoms including developmental and haematologic abnormalities [138]. Leukaemia, hepatocellular carcinoma and squamous cell carcinoma all occur at elevated frequencies. At the subcellular level,

cell cycle disturbances, spontaneous chromosome instability and hypersensitivity to cross-linking agents are all observed.

Eight Fanconi anaemia complementation groups (A–H) have been identified [139]. Germline mutations have been identified in the genes from groups A, C and G [138, 140]. The molecular functions of these three genes are unclear and, unlike other human genes involved in DNA repair and stability, they show no sequence homologies to yeast.

XPD, *XPB*, *XPA*: xeroderma pigmentosum

Xeroderma pigmentosum (XP) is an autosomal recessive disorder characterised by UV sensitivity and the development of basal cell and squamous cell carcinomas. Increased risk of leukaemia and tumours of the stomach, brain and lung have been reported. XP is also associated with various neurologic abnormalities in some patients, including deafness and mental subnormality [7].

XP is caused by germline mutation of one of seven complementation groups (*XP-A* to *XP-G*) involved in nucleotide excision repair (NER) of damaged or mispaired nucleotides [141]. Two of the XP proteins, XPB and XPD, are helicases in the TFIIH transcription complex [142] which is required for both NER and general transcription initiation [143].

A subset of mutations in the *XP* genes leads not to cancer susceptibility but to the neurodevelopment disease Cockayne syndrome and the brittle-hair disorder trichothiodystrophy. Recent evidence suggests that these non-cancer clinical phenotypes are consequences not of perturbed NER, but of the altered transcription activity of the TFIIH complex [144].

ATM: ataxia telangiectasia

Ataxia telangiectasia (AT) is an autosomal recessive disorder caused by mutation of the *ATM* gene on chromosome 11q22.3. It is characterised clinically by progressive neuromotor dysfunction resulting from gradual cerebellar cortical atrophy and variable abnormal cutaneous features that include telangiectasia (dilated blood vessels), vitiligo and café-au-lait macules. Endocrine dysfunction, immunodeficiency, radiation hypersensitivity and cancer susceptibility are other features of this disorder. One-third of AT patients develop cancer, in particular T cell lymphoma and chronic lymphocytic leukaemia (CLL). AT may also be associated with an increased incidence of gastric cancer, medulloblastomas, gliomas, early-onset basal cell carcinomas and uterine cancers. Heterozygotes for *ATM* mutations have an approximately two- to threefold increased risk of breast cancer [145] and may also have increased susceptibility to CLL [146, 147].

AT cells show increased chromosomal instability, a lower capacity to rejoin double-stranded DNA breaks [reviewed in ref. 148], and an inability to arrest DNA synthesis at the G1-S boundary after irradiation. Unlike normal cells that show an increase in the amount and transcriptional activity of p53 following irradiation, little change in p53 activity is observed in AT cells [149].

The ATM protein is a member of a family of homologous serine/threonine protein kinases [150]. In response to ionising (but not UV) radiation, the N terminus of p53 is phosphorylated on serine residue 15 by ATM [151, 152]. This phosphorylation event is likely to contribute to p53 stability by inhibiting its interaction with mdm2 and subsequent degradation [18]. In addition to the phosphorylation of the N terminus, dephosphorylation of C terminus serine residues is important for the activation of p53 following irradiation. This dephosphorylation leads to association of p53 with isoforms of the protein 14-3-3 resulting in increased DNA-binding activity. In AT cells, neither the dephosphorylation event nor the interaction between p53 and 14-3-3 occurs [153]. Since ATM is a kinase, the absence of the dephosphorylation event in AT cells is probably attributable to the loss of an ATM downstream effector. The absence of these p53-dependent events in AT cells results in failure of the cell cycle to arrest. In addition to this p53-dependent cell cycle control, ATM has also been reported to regulate the cell cycle by p53-independent pathways involving c-Abl, replication protein A and the checkpoint 2 protein [154].

A complex between ATM, c-Abl and RAD51, the mammalian homologue of the bacterial recA protein, has recently been identified [reviewed in ref. 155]. RAD51 also interacts with BRCA1 and BRCA2. Both RAD51 and recA are involved in DNA recombination and repair of dsDNA breaks [156].

ATM therefore appears to play a role in the repair of dsDNA breaks by halting the cell cycle until repair is complete and activating the repair process through its interaction with proteins such as RAD51. Consequently, consistent with the clinical features of AT, cells with a higher level of dsDNA breakage, such as germ cells undergoing meiotic recombination, maturing lymphocytes carrying out V(D)J recombination and cells exposed to ionising radiation are more likely to be affected by defective ATM function.

NBS1: Nijmegen breakage syndrome

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disorder that resembles ataxia telangiectasia. It is characterised by microcephaly, growth retardation, endocrine dysfunction, immunodeficiency, radiation hypersensitivity and cancer susceptibility, in particular B cell lymphomas [154]. The gene responsible

for NBS, *NBS1*, has recently been cloned [157, 158]. The *NBS1* product, nibrin, is a novel protein which contains a forkhead transcription factor-associated domain and a BRCT domain [159], both of which have been implicated in cell cycle control and DNA damage repair [160, 161]. Nibrin associates with MRE11 and RAD50, members of a human double-stranded DNA repair complex [162]. Therefore, like its cousin ATM, nibrin appears to play a role in cell cycle regulation and the response to radiation-induced DNA damage [154].

BRCA1/*BRCA2*: familial breast/ovarian cancer

Germline *BRCA1* and *BRCA2* mutations lead to the dominant inheritance of familial breast and ovarian cancer. *BRCA1* mutation carriers have an approximate risk of 80% of developing breast cancer by age 70 and a slightly smaller risk of ovarian cancer [reviewed in ref. 163]. There is also reported to be a three- to fourfold elevated risk of colon cancer and prostate cancer (6 and 8%, respectively) [164]. *BRCA2* mutation carriers have about a similar risk of developing breast cancer by 70 years of age, but the risk of ovarian cancer is probably about half that of *BRCA1* mutation carriers. *BRCA2* families have been reported to have an elevated rate of other neoplasms, including pancreatic cancer, prostate cancer, leukaemia and thyroid cancer. Of families with male breast cancer, 76% contain a *BRCA2* mutation and 16% a mutation in *BRCA1* [163]. Recent evidence suggests that *BRCA1* and *BRCA2* mutations contribute equally to the risk of early-onset breast cancer and an estimated 10% of women diagnosed with breast cancer before 36 years in the United Kingdom carry either a *BRCA1* or *BRCA2* germline mutation [165].

BRCA1 shows limited sequence homology to previously described proteins. It contains a RING zinc finger domain, which is believed to be involved in protein-protein interactions and two BRCT (BRCA1 carboxyl terminus) domains. BRCT domains are found in a number of proteins involved in DNA repair, recombination and checkpoint control [166], but not in BRCA2.

Both BRCA1 and BRCA2 interact with RAD51 [167, 168]. In mitotic human cells BRCA1, RAD51 and the BRCA1-associated protein BARD1 colocalise in discrete foci in the nucleus at S phase [168, 169]. These foci disperse upon DNA damage, concomitant with phosphorylation of BRCA1 [169, 170]. BRCA2-deficient cells show an excessive accumulation of structurally abnormal chromosomes [171] and fibroblasts homozygous for a defective BRCA2 show impaired ds-DNA repair [172]. Both BRCA1- and BRCA2-deficient cells are sensitive to ionising radiation and other genotoxic agents [167, 169, 171].

In addition to their role in genome stability, BRCA1 and BRCA2 have also been implicated in the transcriptional control of cell proliferation [173–175]. Notably, overexpression of *BRCA1* can induce transcription of *GADD45* [176] and the p53 target gene $P21^{CIP1}$ [177]. *GADD45* induction results in activation of the JNK/SAPK-dependent apoptotic pathway [176].

Of the cancer susceptibility syndromes that have been implicated in the maintenance of genome stability, only the BRCA1/2 syndromes do not show a recessive pattern of inheritance. The relative rarity of haematological malignancies in BRCA1/2 families also sets them apart from the other syndromes characterised by genome instability. These differences emphasise the likelihood of functions for BRCA1/2 which are unrelated to the cellular response to damage from ionising radiation.

MLH1/*MSH2*/*PMS1*/*PMS2*/*MSH6*: hereditary non-polyposis colorectal cancer

Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant cancer syndrome caused by mutation of one of several DNA mismatch repair genes. To date, mutations have been identified in *MLH1*, *MSH2*, *PMS1*, *PMS2* and *MSH6* [reviewed in ref. 178], although *MLH1* and *MSH2* account for more than 90% of the germline HNPCC mutations identified to date. Each of these repair proteins are homologues of the *E. coli* mutHLS DNA repair complex. The mutHLS complex is able to correct base-base mispairs and insertion/deletion loops of up to four nucleotides [179].

Mutation carriers have a lifetime risk of about 50% (female)–80% (male) of developing colorectal cancer and a 60% risk of endometrial cancer [180]. There is also an increased risk of a number of other cancers including ovarian, gastric, pancreatic, and sebaceous carcinomas and glioblastomas [7]. Mutations in *MSH6*, although uncommon, appear to result in an atypical, milder phenotype with a predominance of extracolonic cancers [181, 182].

The hallmark of HNPCC tumours is the replication error phenotype (RER +). Loss of mismatch repair renders a cell prone to insertion/deletion mutations, particularly at sites of nucleotide repeats. The presence of short runs of mono- or dinucleotide repeats within coding sequences provides potential mutation hotspots. Analyses of gastrointestinal tumours displaying the RER + phenotype have identified a high frequency of insertions/deletions in repeat sequences within the coding sequences of the genes for IGF2R [183], the E2F4 transcription factor [184], the pro-apoptotic protein Bax [185, 186] and the type II transforming growth-factor (TGF)-β receptor [81]. Mutation of the type II TGF-β receptor is predicted to give a selective advantage by providing a means for escaping TGF-β-mediated growth control [81]. Strikingly, mutations in the type II

TGF-β receptor and *E2F4* genes, although common in gastric and colon cancers, are rare in RER + endometrial cancers [184, 187], suggesting that endometrial RER + tumours progress via a distinct genetic mechanism. Insertions/deletions in other oncogenes and tumour suppressor genes, such as *CDX2*, the human homologue of the *Drosophila* homeobox gene *caudal* [188] are also likely to contribute to the clonal evolution of tumours lacking mismatch repair activity.

Concluding remarks

The study of inherited cancer susceptibility has made a profound contribution to the elucidation of tumorigenesis by enabling the identification of genes whose altered or abrogated expression are causes, and not simply consequences, of cancer. However, significant challenges remain. First, the identification of susceptibility genes has done little to explain the tissue spectrums of the cancer syndromes. In some syndromes, the spectrum may reflect the lack of functional redundancy in the affected tissues. However, in others it will reflect unknown interactions between the susceptibility genes and proliferative or survival pathways that are largely tissue specific. Insight into these interactions will be critical to the evolution of a new generation of cancer therapies with tissue-specific activity. A second challenge is the identification of low-penetrance susceptibility genes and an understanding of the environmental and/or genetic factors that dictate this penetrance. Similarly, a better understanding of the factors that influence the age of disease onset in cancer families is also required. Although much of this variation will be attributable to random differences in the time taken for additional rare somatic mutations to occur, genetic background and environmental triggers would be predicted to be significant modifiers.

Acknowledgements. Thanks to Fernanda da Silva Tatley for critical reading of the manuscript and Sue Cleverley for expert assistance with manuscript preparation.

1 Hengstler J., Arand M., Herrero M. and Oesch F. (1998) Polymorphisms of N-acetyltransferases, glutathione S-transferases, microsomal epoxide hydrolase and sulfotransferases: influence on cancer susceptibility. Rec. Results Cancer Res. **154:** 47–85
2 Haber D. and Harlow E. (1997) Tumour-suppressor genes: evolving definitions in the genomic age. Nat. Genet. **16:** 320–322
3 Knudson A. G. (1971) Mutation and cancer: statistical study of retinoblastoma. Proc. Natl. Acad. Sci. USA **68:** 820–823
4 Stiegler P., Kasten M. and Giodano A. (1998) The RB family of cell cycle regulatory factors. J. Cell. Biochem. **30/31:** 30–36
5 Adams P. D. and Kaelin W. G. (1998) Negative control elements of the cell cycle in human tumors. Curr. Biol. **10:** 791–797
6 Soufir N., Avril M.-F., Chompret A., Demenais F., Bombled J., Spatz A. et al. (1998) Prevalence of p16 and CDK4 germline mutations in 48 melanoma-prone families in France. Hum. Mol. Genet. **7:** 209–216
7 Lindor N. M., Greene M. H. and Program M. F. C. (1998) The concise handbook of family cancer syndromes. J. Natl. Cancer Inst. **90:** 1039–1071
8 Hall M., Bates S. and Peters G. (1995) Evidence for different modes of action of cyclin-dependent kinase inhibitors: p15 and p16 bind to kinases, p21 and p27 bind to cyclins. Oncogene **11:** 1581–1588
9 Wölfel T., Hauer M., Schneider J., Serrano M., Wölfel C., Klehmann-Hieb E. et al. (1995) A $p^{16INK4a}$-insensitive CDK4 mutant targeted by cytolytic T lymphocytes in a human melanoma. Science **269:** 1281–1284
10 Zuo L., Weger J., Yang Q., Goldstein A. M., Tucker M. A., Walker G. J. et al. (1996) Germline mutations in the $p16^{INK4a}$ binding domain of CDK4 in familial melanoma. Nat. Genet. **12:** 97–99
11 Sharpless N. E. and DePinho R. A. (1999) The INK4A/ARF locus and its two gene products. Curr. Opin. Genet. Dev. **9:** 22–30
12 Quelle D. E., Cheng M., Ashmun R. A. and Sherr C. J. (1997) Cancer-associated mutations at the *INK4a* locus cancel cell cycle arrest by $p^{16INK4a}$ but not by the alternative reading frame protein p19ARF. Proc. Natl. Acad. Sci. USA **94:** 669–673
13 Gruis N. A., Velden P. A. van der, Sandkuijl L. A., Prins D. E., Weaver-Feldaus J., Kamb A. et al. (1995) Homozygotes for *CDKN2* (p16) germline mutation in Dutch familial melanoma kindreds. Nat. Genet. **10:** 351–353
14 Ruas M. and Peters G. (1998) The $p16^{INK4a}$/CDKN2A tumor suppressor and its relatives. Biochim. Biophys. Acta **1378:** F115–F177
15 Palmero I., McConnell B., Parry D., Brookes S., Hara E., Bates S. et al. (1997) Accumulation of $p16^{INK4a}$ in mouse fibroblasts as a function of replicative senescence and not of retinoblastoma gene status. Oncogene **15:** 495–503
16 Zindy F., Quelle D. E., Roussel M. F. and Sherr C. J. (1997) Expression of the $p16^{INK4a}$ tumor suppressor versus other INK4 family members during mouse development and aging. Oncogene **15:** 203–211
17 Vogt M., Haggblom C., Yeargin J., Christiansen-Weber T. and Haas M. (1998) Independent induction of senescence by $p16^{INK4a}$ and $p21^{CIP1}$ in spontaneously immortalized human fibroblasts. Cell Growth Differ. **9:** 139–146
18 Prives C. (1998) Signaling to p53: breaking the MDM2-p53 circuit. Cell **95:** 5–8
19 Chen J., Lin J. and Levine A. J. (1995) Regulation of transcription functions of the p53 tumor suppressor by the *mdm-2* oncogene. Mol. Med. **1:** 142–152
20 Kubbutat M. H. G., Jones S. N. and Vousden K. H. (1997) Regulation of p53 stability by mdm2. Nature **387:** 299–303
21 Haupt Y., Maya R., Kazaz A. and Oren M. (1997) Mdm2 promotes the rapid degradation of p53. Nature **387:** 296–299
22 El-Deiry W. S., Kern S. E., Pietenpol J. A., Kinzler K. and Vogelstein B. (1992) Definition of a consensus binding site for p53. Nat. Genet. **1:** 45–49
23 Waldman T., Lengauer C., Kinzler K. W. and Vogelstein B. (1996) Uncoupling of S phase and mitosis induced by anticancer agents in cells lacking p21. Nature **381:** 713–716
24 Wang X. W., Zhan Q., Coursen J. D., Khan M. A., Kontny H. U., Yu L. et al. (1999) GADD45 induction of a G_2/M cell cycle checkpoint. Proc. Natl. Acad. Sci. USA **96:** 3706–3711
25 Hermeking H., Lengauer C., Polyak K., He T.-C., Zhang L., Thiagalingam S. et al. (1997) *14-3-3*σ is a p53-regulated inhibitor of G2/M progression. Mol. Cell **1:** 3–11
26 Miyashita T. and Reed J. C. (1995) Tumor suppressor p53 is a direct transcriptional activator of the human *bax* gene. Cell **80:** 293–299
27 Polyak K., Xia Y., Zweier J. L., Kinzler K. W. and Vogelstein B. (1997) A model for p53-induced apoptosis. Nature **389:** 300–305

28 Bennett M., Macdonald K., Chan S.-W., Luzio J. P., Simari R. and Weissberg P. (1998) Cell surface trafficking of Fas: a rapid mechanism of p53-mediated apoptosis. Science **282:** 290–293

29 Birch J. M., Blair V., Kelsey A. M., Evans D. G., Harris M., Tricker K. J. et al. (1998) Cancer phenotype correlates with constitutional TP53 genotype in families with the Li-Fraumeni syndrome. Oncogene **17:** 1061–1068

30 Hamilton S., Liu B., Parsons R., Papadopoulos N., Jen J., Powell S. et al. (1995) The molecular basis of Turcot's syndrome. N. Engl. J. Med. **332:** 839–847

31 Polakis P. (1999) The oncogenic activation of β-catenin. Curr. Opin. Genet. Dev. **9:** 15–21

32 Rubinfeld B., Albert I., Porfiri E., Fiol C., Munemitsu S. and Polakis P. (1996) Binding of GSK3β to the APC-β-catenin complex and regulation of complex assembly. Science **272:** 1023–1026

33 Hart M. J., Santos R. de los, Albert I. N., Rubinfeld B. and Polakis P. (1998) Downregulation of β-catenin by human axin and its association with the APC tumor suppressor, β-catenin and GSK3β. Curr. Biol. **8:** 573–581

34 Behrens J., Jerchow B.-A., Würtele M., Grimm J., Asbrand C., Wirtz R. et al. (1998) Functional interaction of an axin homolog, conduction, with β-catenin, APC and GSK3β. Science **280:** 596–599

35 Tetsu O. and McCormick F. (1999) β-Catenin regulates expression of cyclin D1 in colon carcinoma cells. Nature **398:** 422–426

36 Mann B., Gelos M., Siedow A., Hanski M. L., Gratchev A., Ilyas M. et al. (1999) Target genes of β-catenin-T cell-factor/lymphoid-enhancer-factor signaling in human colorectal carcinomas. Proc. Natl. Acad. Sci. USA **96:** 1603–1608

37 Gradl D., Kühl M. and Wedlich D. (1999) The Wnt/Wg signal transducer β-catenin controls fibronectin expression. Mol. Cell. Biol. **19:** 5576–5587

38 Huber O., Bierkamp C. and Kemler R. (1996) Cadherins and catenins in development. Curr. Opin. Cell Biol. **8:** 685–691

39 Novak A., Hsu S.-C., Leung-Hagesteijn C., Radeva G., Papkoff J., Montesano R. et al. (1998) Cell adhesion and the integrin-linked kinase regulate the LEF-1 and β-catenin signaling pathways. Proc. Natl. Acad. Sci. USA **95:** 4374–4379

40 Hulsken J., Birchmeier W. and Behrens J. (1994) E-cadherin and APC compete for the interaction with β-catenin and the cytoskeleton. J. Cell Biol. **127:** 2061–2069

41 Rubinfeld B., Souza B., Albert I., Munemitsu S. and Polakis P. (1995) The APC protein and E-cadherin form similar but independent complexes with α-catenin, β-catenin, and plakoglobin. J. Biol. Chem. **270:** 5549–5555

42 Wasan H. S., Park H.-S., Liu K. C., Mandir N. K., Winnett A., Sasieni P. et al. (1998) APC in the regulation of intestinal crypt fission. J. Pathol. **185:** 246–255

43 Narayan S. and Jaiswal A. S. (1997) Activation of adenomatous polyposis coli (APC) gene expression by the DNA-alkylating agent N-methyl-N′-nitro-N-nitrosoguanidine requires p53. J. Biol. Chem. **272:** 30619–30622

44 Spirio L., Olschwang S., Groden J., Robertson M., Samowitz W., Joslyn G. et al. (1993) Alleles of the APC gene: an attenuated form of familial polyposis. Cell **75:** 951–957

45 Friedl W., Meuschel S., Caspari R., Lamberti C., Krieger S., Sengteller M. et al. (1996) Attentuated familial adenomatous polyposis due to a mutation in the 3′ part of the APC gene: a clue for understanding the function of the APC protein. Hum. Genet. **97:** 579–584

46 Luijt R. B. van der, Meera K. P., Vasen H. F., Breukel C., Tops C. M., Scott R. J. et al. (1996) Germline mutations in the 3′ part of APC exon 15 do not result in truncated proteins and are associated with attenuated adenomatous polyposis coli. Hum. Genet. **98:** 727–734

47 Laken S. J., Petersen G. M., Gruber S. B., Oddoux C., Ostrer H., Giariello F. M. et al. (1997) Familial colorectal cancer in Ashkenazim due to a hypermutable tract in APC. Nat. Genet. **17:** 79–83

48 Gryfe R., Nicola N. D., Lal G., Gallinger S. and Redston M. (1999) Inherited colorectal polyposis and cancer risk of the APC I1307K polymorphism. Am. J. Hum. Genet. **64:** 378–384

49 Frayling I. M., Beck N. E., Ilyas M., Dove-Edwin I., Goodman P., Pack K. et al. (1998) The *APC* variants I1307K and E1317Q are associated with colorectal tumors, but not always with a family history. Proc. Natl. Acad. Sci. USA **95:** 10722–10727

50 Guilford P., Hopkins J., Harraway J., McLeod M., McLeod N., Harawira P. et al. (1998) E-cadherin germline mutations in familial gastric cancer. Nature **392:** 402–405

51 Guilford P., Hopkins J., Grady W., Markowitz S., Willis J., Lynch H. et al. (1999) E-cadherin germline mutations define an inherited cancer syndrome dominated by diffuse gastric cancer. Hum. Mutat. **14:** 249–255

52 Richards F. M., McKee S. A., Rajpar M. H., Cole T. R. P., Evans D. G. R., Jankowski J. A. et al. (1999) Germline E-cadherin gene (CDH1) mutations predispose to familial gastric cancer and colorectal cancer. Hum. Mol. Genet. **8:** 607–610

53 Keller G., Vogelsang H., Becker I., Hutter J., Ott K., Candidus S. et al. (1999) Diffuse type gastric and lobular breast carcinoma in a familial gastric cancer patient with an E-cadherin germline mutation. Am. J. Pathol. **155:** 337–342

54 Gayther S. A., Gorringe K. L., Ramus S. J., Huntsman D., Roviello F., Grehan N. et al. (1998) Identification of germline E-cadherin mutations in gastric cancer families of European origin. Cancer Res. **58:** 4086–4089

55 Grunwald G. B. (1993) The structural and functional analysis of cadherin calcium-dependent cell adhesion molecules. Curr. Opin. Cell Biol. **5:** 797–805

56 Behrens J., Mareel M. M., Roy F. M. van and Birchmeier W. (1989) Dissecting tumor cell invasion: epithelial cells acquire invasive properties after the loss of uvomorulin-mediated cell-cell adhesion. J. Cell Biol. **108:** 2435–2447

57 Frixen E. H., Behrens J., Sachs M., Eberle G., Voss B., Warda A. et al. (1991) E-cadherin-mediated cell-cell adhesion prevents invasiveness of human carcinoma cells. J. Cell Biol. **113:** 173–185

58 Vleminckx K., Vakaet L., Mareel M., Fiers W. and Roy F. van (1991) Genetic manipulation of E-cadherin expression by epithelial tumor cells reveals an invasion suppressor role. Cell **66:** 107–119

59 Perl A.-K., Wilgenbus P., Dahl U., Semb H. and Christofori G. (1998) A causal role for E-cadherin in the transition from adenoma to carcinoma. Nature **392:** 190–193

60 Guilford P. (1999) E-cadherin downregulation in cancer: fuel on the fire? Mol. Med. Today **5:** 172–177

61 Sadot E., Simcha I., Shtutman M., Ben-Ze'ev A. and Geiger B. (1998) Inhibition of β-catenin mediated transactivation by cadherin derivatives. Proc. Natl. Acad. Sci. USA **95:** 15339–15344

62 Caca K., Kolligs F. T., Ji X., Hayes M., Qian J.-M., Yahanda A. et al. (1999) β- and γ-catenin mutations, but not E-cadherin inactivation, underlie T-cell factor/lymphoid enhancer factor transcriptional deregulation in gastric and pancreatic cancer. Cell Growth Differ. **10:** 369–376

63 Boardman L. A., Thibodeau S. N., Schaid D. J., Lindor N. M., McDonnell S. K., Burgard L. J. et al. (1998) Increased risk for cancer in patients with the Peutz-Jeghers syndrome. Ann. Intern. Med. **128:** 896–899

64 Mehenni H., Gehrig C., Nezu J.-i., Oku A., Shimane M., Rossier C. et al. (1998) Loss of LKB1 kinase activity in Peutz-Jeghers syndrome, and evidence for allelic and locus heterogeneity. Am. J. Hum. Genet. **63:** 1641–1650

65 Ylikorkala A., Avizienyte E., Tomlinson I. P. M., Tiainen M., Roth S., Loukola A. et al. (1999) Mutations and impaired function of LKB-1 in familial and non-familial Peutz-Jeghers syndrome and a sporadic testicular cancer. Hum. Mol. Genet. **8:** 45–51

66 Hemminki A., Markie D., Tomlinson I., Avizienyte E., Roth S., Loukola A. et al. (1998) A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature **391:** 184–187

67 Jenne D. E., Reimann H., Nezu J., Friedel W., Loff S., Jeschke R. et al. (1998) Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nat. Genet. **18:** 38–43

68 Avizienyte E., Loukola A., Roth S., Hemminki A., Tarkkanen M., Salovaara R. et al. (1999) LKB1 somatic mutations in sporadic tumours. Am. J. Pathol. **154:** 677–681

69 Olschwang S., Serova-Sinilnikova O. M., Lenoir G. M. and Thomas G. (1998) PTEN germ-line mutations in juvenile polyposis coli. Nat. Genet. **18:** 12–14

70 Myers M. P., Stolarov J. P., Eng C., Li J., Wang S. I., Wigler M. H. et al. (1997) PTEN, the tumor suppressor from human chromosome 10q23, is a dual specificity phosphatase. Proc. Natl. Acad. Sci. USA **94:** 9052–9057

71 Maehama T. and Dixon J. E. (1998) The tumor suppressor, PTEN/NMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J. Biol. Chem. **273:** 13375–13378

72 Kulik G., Klippel A. and Weber M. (1997) Antiapoptotic signaling by the insulin-like growth factor receptor, phoshatidylinositol 3-kinase, and Akt. Mol. Cell. Biol. **17:** 1595–1606

73 Ahmed N. N., Grimes H. L., Bellacosa A., Chan T. O. and Tsichlis P. N. (1997) Transduction of interleukin-2 antiapoptotic and proliferative signals via Akt protein kinase. Proc. Natl. Acad. Sci. USA **94:** 3627–3632

74 Khwaja A., Rodriguez-Viciana P., Wennstrom S., Warne P. H. and Downward J. (1997) Matrix adhesion and Ras transformation both activate a phosphoinositide 3-OH kinase and protein kinase B/Akt cellular survival pathway. EMBO J. **16:** 2783–2793

75 Kauffman-Zeh A., Rodriguez-Viciana P., Ulrich E., Gilbert C., Coffer P., Downward J. et al. (1997) Suppression of c-Myc-induced apoptosis by Ras signaling through PI(3)K and PKB. Nature **385:** 544–548

76 Wu X., Senechal K., Neshat M. S., Whang Y. E. and Sawyers C. L. (1998) The PTEN/NMAC1 tumor suppressor phosphatase functions as a negative regulator of the phosphoinositide 3-kinase/Akt pathway. Proc. Natl. Acad. Sci. USA **95:** 15587–15591

77 Stambolic V., Suzuki A., Pompa J. L. de la, Brothers G. M., Mirtsos C., Sasaki T. et al. (1998) Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. Cell **95:** 29–39

78 Li D.-M. and Sun H. (1998) PTEN/NMAC1/TEP1 suppresses the tumorigenicity and induces G1 cell cycle arrest in human glioblastoma cells. Proc. Natl. Acad. Sci. USA **95:** 15406–15411

79 Tamura M., Gu J., Danen E. H., Takino T., Miyamoto S. and Yamada K. M. (1999) PTEN interactions with focal adhesion kinase and suppression of the extracellular matrix-dependent phosphatidylinositol 3-kinase/Akt cell survival pathway. J. Biol. Chem. **274:** 20693–20703

80 Howe J. R., Roth S., Ringold J. C., Summers R. W., Järvinen H. J., Sistonen P. et al. (1998) Mutations in the *SMAD4/DPC4* gene in juvenile polyposis. Science **280:** 1086–1088

81 Markowitz S., Wang J., Myeroff L., Parsons R., Sun L., Lutterbaugh J. et al. (1995) Inactivation of the type II TGF-β receptor in colon cancer cells with microsatellite instability. Science **268:** 1336–1338

82 Zawel L., Dai J. L., Buckhaults P., Zhou S., Kinzler K. W., Vogelstein B. et al. (1998) Human Smad3 and Smad4 are sequence-specific transcription activators. Mol. Cell **1:** 611–617

83 Liberati N. T., Datto M. B., Frederick J. P., Shen X., Wong C., Rougier-Chapman E. M. et al. (1999) Smads bind directly to the Jun family of AP-1 transcription factors. Proc. Natl. Acad. Sci. USA **96:** 4844–4849

84 Datto M. B., Li Y., Panus J. F., Howe D. J., Xiong Y. and Wang X.-F. (1995) Transforming growth factor β induces the cyclin-dependent kinase inhibitor p21 through a p53-independent mechanism. Proc. Natl. Acad. Sci. USA **92:** 5545–5549

85 Hannon G. J. and Beach D. (1994) $p15^{INK4B}$ is a potential effector of TGF-β-induced cell cycle arrest. Nature **371:** 257–261

86 Keeton M. R., Curriden S. A., Zonneveld A. J. van and Loskutoff D. J. (1991) Identification of regulatory sequences in the type 1 plasminogen activator inhibitor gene responsive to transforming growth factor β. J. Biol. Chem. **266:** 23048–23052

87 Bassett J. H. D., Forbes S. A., Pannett A. A. J., Lloyd S. E., Christie P. T., Wooding C. et al. (1998) Characterization of mutations in patients with multiple endocrine neoplasia type 1. Am. J. Hum. Genet. **62:** 232–244

88 Giraud S., Zhang C. X., Serova-Sinilnikova O., Wautot V., Salandre J., Buisson N. et al. (1998) Germ-line mutation analysis in patients with multiple endocrine neoplasia type 1 and related disorders. Am. J. Hum. Genet. **63:** 455–467

89 Agarwal S. K., Guru S. C., Heppner C., Erdos M. R., Colins R. M., Park S. Y. et al. (1999) Menin interacts with the AP1 transcription factor JunD and represses JunD-activated transcription. Cell **96:** 143–152

90 Santoro M., Carlomagno F., Romano A., Bottaro D. P., Dathan N. A., Grieco M. et al. (1995) Activation of RET as a dominant transforming gene by germline mutations of MEN2A and MEN2B. Science **267:** 381–383

91 Mulligan L. M., Eng C., Healey C. S., Clayton D., Kwok J. B. J., Gardner E. et al. (1994) Specific mutations of the *RET* proto-oncogene are related to disease phenotype in MEN 2A and FMTC. Nat. Genet. **6:** 70–74

92 Ponder B. A. J. (1999) The phenotypes associated with *ret* mutations in the multiple endocrine neoplasia type 2 syndrome. Cancer Res. **59:** 1736s–1741s

93 Decker R. A., Peacock M. L. and Watson P. (1998) Hirschsprung disease in MEN 2A: increased spectrum of *RET* exon 10 genotypes and strong genotype-phenotype correlation. Hum. Mol. Genet. **7:** 129–134

94 Jeffers M., Schmidt L., Nakaigawa N., Webb C. P., Weirich G., Kishida T. et al. (1997) Activating mutations for the met tyrosine kinase receptor in human cancer. Proc. Natl. Acad. Sci. USA **94:** 11445–11450

95 Schmidt L., Duh F.-M., Chen F., Kishida T., Glenn G., Choyke P. et al. (1997) Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat. Genet. **16:** 68–73

96 Moriyama Y., Tsujimura T., Hashimoto K., Morimoto M., Kitayama H., Matsuzawa et al. (1996) Role of aspartic acid 814 in the function and expression of c-kit receptor tyrosine kinase., J. Biol. Chem. **271:** 3347–3350

97 Bottaro D. P., Rubin J. S., Faletto D. L., Chan A. M., Kmiecik R. E., Vande Woude G. F. et al. (1991) Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product. Science **251:** 802–804

98 Sonnenberg E., Meyer D., Weidner K. M. and Birchmeier C. (1993) Scatter factor/hepatocyte growth factor and its receptor, the c-met tyrosine kinase, can mediate a signal exchange between mesenchyme and epithelia during mouse development. J. Cell Biol. **123:** 223–235

99 Weidner K. M., Sachs M. and Birchmeier W. (1993) The Met receptor tyrosine kinase transduces motility, proliferation and morphogenic signals of scatter factor/hepatocyte growth factor in epithelial cells. J. Cell Biol. **121:** 145–154

100 Jeffers M., Fiscella M., Webb C. P., Anver M., Koochekpour S. and Woude G. F. V. (1998) The mutationally activated Met receptor mediates motility and metastasis. Proc. Natl. Acad. Sci. USA **95:** 14417–14422

101 Nishida T., Hirota S., Taniguchi M., Hashimoto K., Isozaki K., Makamura H. et al. (1998) Familial gastrointestinal stromal tumours with germline mutation of the *KIT* gene. Nat. Genet. **19:** 323–324

102 Hammerschmidt M., Brook A. and McMahon A. P. (1997) The world according to *hedgehog*. Trends Genet. **13:** 14–21

103 Kim H., Ling B. and Ratner N. (1997) Nf1-deficient mouse Schwann cells are angiogenic and invasive and can be induced to hyperproliferate: reversion of some phenotypes by

an inhibitor of farnesyl protein transferase. Mol. Cell. Biol. **17:** 862–872
104 Marchuk D. A., Saulino A. M., Tavakkol R., Swaroop M., Wallace M. R., Andersen L. B. et al. (1991) cDNA cloning of the type 1 neurofibromatosis gene: complete sequence of the *NF1* gene product. Genomics **11:** 931–940
105 Gutmann D. H. and Collins F. S. (1993) The neurofibromatosis type 1 gene and its protein product, neurofibromin. Neuron **10:** 335–343
106 Klose A., Ahmadian M. R., Schuelke M., Scheffzek K., Hoffmeyer S., Gewies A. et al. (1998) Selective disactivation of neurofibromin GAP activity in neurofibromatosis type 1 (NF1). Hum. Mol. Genet. **7:** 1261–1268
107 Bourne H. R., Sanders D. A. and McCormick F. (1991) The GTPase superfamily: conserved structure and molecular mechanism. Nature **349:** 117–127
108 DeClue J. E., Papageorge A. G., Fletcher J. A., Diehl S. R., Ratner N., Vass W. C. et al. (1992) Abnormal regulation of mammalian $p21^{ras}$ contributes to malignant tumor growth in von Recklinghausen (type 1) neurofibromatosis. Cell **69:** 265–273
109 Xu G., Lin B., Tanaka K., Dunn D., Wood D., Gesteland R. et al. (1990) The catalytic domain of the neurofibromatosis type-1 gene product stimulates *ras* GTPase and complements *ira* mutants of *S. cerevisiae*. Cell **63:** 835–841
110 Cobb M. H. and Goldsmith E. J. (1995) How MAP kinases are regulated. J. Biol. Chem. **270:** 14843–14846
111 Marshall C. J. (1995) Specificity of receptor tyrosine kinase signaling: transient versus sustained extracellular signal-regulated kinase activation. Cell **80:** 179–185
112 Marais R., Wynne J. and Treisman R. (1993) The SRF accessory protein Elk-1 contains a growth factor-regulated transcriptional activation domain. Cell **73:** 381–393
113 Rouleau G. A., Merel P., Lutchman M., Sanson M., Zucman J., Marineau C. et al. (1993) Alteration in a new gene encoding a putative membrane-organizing protein causes neurofibromatosis type 2. Nature **363:** 515–521
114 Trofatter J. A., MacCollin M. M., Rutter J., Murrell J., Duyao M., Parry D. et al. (1993) A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. Cell **72:** 791–800
115 Parry D., MacCollin M., Kaiser-Kupfer M., Pulaski K., Nicholson H., Bolesta M. et al. (1996) Germ-line mutations in the neurofibromatosis 2 gene: correlations with disease severity and retinal abnormalities. Am. J. Hum. Genet. **59:** 529–539
116 Ruttledge M., Andermann A., Phelan C., Claudio J., Han F., Chretien N. et al. (1996) Type of mutation in the neurofibromatosis type 2 gene (NF2) frequently determines severity of disease. Am. J. Hum. Genet. **59:** 331–342
117 Gonzalez-Agosti C., Xu L., Pinney D., Beauchamp R., Hobbs W., Gusella J. et al. (1996) The merlin tumor suppressor localizes preferentially in membrane ruffles. Oncogene **13:** 1239–1247
118 Shaw R. J., McClatchey A. I. and Jacks T. (1998) Regulation of the neurofibromatosis type 2 tumor suppressor protein, merlin, by adhesion and growth arrest stimuli. J. Biol. Chem. **273:** 7757–7764
119 Maher E. and Kaelin W. G. (1997) von Hippel-Lindau disease. Medicine **76:** 381–391
120 Duan D. R., Pause A., Burgress W., Aso T., Chen D. Y. T., Garrett K. P. et al. (1995) Inhibition of transcriptional elongation by the VHL tumor suppressor protein. Science **269:** 1402–1406
121 Kaelin W. G. and Maher E. R. (1998) The VHL tumour-suppressor gene paradigm. Trends Genet. **14:** 423–426
122 Iliopoulos O., Jiang C., Levy A. P., Kaelin W. G. and Goldberg M. A. (1996) Negative regulation of hypoxia-inducibile genes by the von Hippel-Lindau protein. Proc. Natl. Acad. Sci. USA **93:** 10595–10599
123 Kim K., Katayose Y., Li Q., Rakkar A. N., Li Z., Hwang S. G. et al. (1998) Recombinant adenovirus expressing Von Hippel-Lindau-mediated cell cycle arrest is associated with the induction of cyclin-dependent kinase inhibitor p27Kip1. Biochem. Biophys. Res. Commun. **253:** 672–677
124 Ohh M., Yauch R. L., Lonergan K. M., Whaley J. M., Stemmer-Rachamimov A. O., Louis D. N. et al. (1998) The von-Hippel-Lindau tumor suppressor protein is required for proper assembly of an extracellular fibronectin matrix. Mol. Cell **1:** 959–968
125 Gorospe M., Egan J. M., Zbar B., Lerman M., Geil L., Kuzmin I. et al. (1999) Protective function of von Hippel-Lindau protein against impaired protein processing in renal carcinoma cells. Mol. Cell. Biol. **19:** 1289–1300
126 Pause A., Peterson B., Schaffar G., Stearman R. and Klausner R. D. (1999) Studying interactions of four proteins in the yeast two-hybrid system: structural resemblance of the pVHL/elongin BC/hCUL-2 complex with the ubiquitin ligase complex SKP1/cullin/F-box protein. Proc. Natl. Acad. Sci. USA **96:** 9533–9538
127 Lonergan K. M., Iliopoulos O., Ohh M., Kamura T., Conaway R. C., Conaway J. W. et al. (1998) Regulation of hypoxia-inducibile mRNAs by the von Hippel-Lindau tumor suppressor protein requires binding to complexes containing elongins B/C and Cul2. Mol. Cell. Biol. **18:** 732–741
128 Fraizer G. C., Wu Y. J., Hewitt S. M., Maity T., Ton C. C., Huff V. et al. (1994) Transcriptional regulation of the human Wilms' tumor gene (WT1): cell type-specific enhancer and promiscuous promoter. J. Biol. Chem. **269:** 8892–8900
129 Oji Y., Ogawa H., Tamaki H., Oka T., Tsuboi A., Kim E. H. et al. (1999) Expression of the Wilms' tumor gene *WT1* in solid tumors and its involvement in tumor cell growth. Jpn. J. Cancer Res. **90:** 194–204
130 Drummond I. A., Madden S. L., Rohwer Nutter P., Bell G. I., Sukhatme V. P. and Rauscher F. J. (1992) Repression of the insulin-like growth factor II gene by the Wilms tumor suppressor WT1. Science **257:** 674–678
131 Werner H., Re G. G., Drummond I. A., Sukhatme V. P., Rauscher F. J., Sens D. A. et al. (1993) Increased expression of the insulin-like growth factor I receptor gene, IGF1R, in Wilms tumor is correlated with modulation of IGF1R promoter activity by the WT1 Wilms tumor gene product. Proc. Natl. Acad. Sci. USA **90:** 5828–5832
132 Ryan G., Steele-Perkins V., Morris J. F., Rauscher F. J. and Dressler G. R. (1995) Repression of Pax-2 by WT1 during normal kidney development. Development **121:** 867–875
133 Englert C. (1998) WT1 – more than a transcription factor?, Trends Biochem. Sci. 389–393
134 Caricasole A., Duarte A., Larsson S. H., Hastie N. D., Little M., Holmes G. et al. (1996) RNA binding by the Wilms tumor suppressor zinc finger proteins. Proc. Natl. Acad. Sci. USA **93:** 7562–7566
135 Kusano K., Berres M. and Engels W. (1999) Evolution of the RECQ family of helicases: a *Drosophila* homolog, Dmblm, is similar to the human Bloom syndrome gene. Genetics **151:** 1027–1039
136 Davey S., Han C. S., Ramer S. A., Klassen J. C., Jacobson A., Eisenberger A. et al. (1998) Fission yeast rad12+ regulates cell cycle checkpoint control and is homologous to the Bloom's syndrome disease gene. Mol. Cell. Biol. **18:** 2721–2728
137 Matsumoto T., Shinamoto A., Goto M. and Furuichi Y. (1997) Impaired nuclear localisation of defective DNA helicases in Werner's syndrome. Nat. Genet. **16:** 335–336
138 Carreau M. and Buchwald M. (1998) Fanconi's anemia: what have we learned from the genes so far? Mol. Med. Today **4:** 201–206
139 Joenje H., Oostra A. B., Wijker M., Summa F. M. di, Berkel C. G. van, Rooimans M. A. et al. (1997) Evidence for at least eight Fanconi anemia genes. Am. J. Hum. Genet. **61:** 940–944
140 Winter J. P. de, Waisfisz Q., Rooimans M. A., Berkel C. G. M. v., Bosnoyan-Collins L., Alon N. et al. (1998) The Fanconi anaemia group G gene FANCG is identical with XRCC9. Nat. Genet. **20:** 281–283

141 Sancar A. (1999) Excision repair invades the territory of mismatch repair. Nat. Genet. **21:** 247–249
142 Steeg H. van and Kraemer K. (1999) Xeroderma pigmentosum and the role of UV-induced DNA damage in skin cancer. Mol. Med. Today **5:** 86–94
143 Winkler G. S. and Hoeijmakers J. H. J. (1998) From a DNA helicase to brittle hair. Nat. Genet. **20:** 106–107
144 Coin F., Marinoni J.-C., Rodolfo C., Fribourg S., Pedrini A. M. and Egly J.-M. (1998) Mutations in the XPD helicase gene result in XP and TTD phenotypes, preventing interaction between XPD and the p44 subunit of TFIIH. Nat. Genet. **20:** 184–188
145 Inskip H. M., Kinlen L. J., Taylor A. M. R., Woods C. G. and Arlett C. F. (1999) Risk of breast cancer and other cancers in heterozygotes for ataxia-telangiectasia. Br. J. Cancer **79:** 1304–1307
146 Stankovic T., Weber P., Stewart G., Bedenham T., Murray J., Byrd P. J. et al. (1999) Inactivation of ataxia telangiectasia mutated gene in B-cell chronic lymphocytic leukaemia. Lancet **353:** 26–29
147 Bevan S., Yuille M. R., Marossy A., Catovsky D. and Houlston R. S. (1999) Ataxia telangiectasia gene mutations and chronic lymphocytic leukaemia. Lancet **353:** 753
148 Jeggo P. A., Carr A. M. and Lehmann A. R. (1998) Splitting the ATM: distinct repair and checkpoint defects in ataxia-telangiectasia. Trends Genet. **14:** 312–316
149 Kastan M. B., Zhan Q., el-Deiry W. S., Carrier F., Jacks T., Walsh W. V. et al. (1992) A mammalian cell cycle checkpoint pathway utilizing p53 and GADD45 is defective in ataxia-telangiectasia. Cell **71:** 587–597
150 Canman C. E. and Lim D.-S. (1998) The role of ATM in DNA damage responses and cancer. Oncogene **17:** 3301–3308
151 Banin S., Moyal L., Shieh S.-Y., Taya Y., Anderson C. W., Chessa L. et al. (1998) Enhanced phosphorylation of p53 by ATM in response to DNA damage. Science **281:** 1674–1677
152 Canman C. E., Lim D.-S., Cimprich K. A., Taya Y., Tamai K., Sakaguchi K. et al. (1998) Activation of the ATM kinase by ionizing radiation and phosphorylation of p53. Science **281:** 1677–1699
153 Waterman M. J. F., Stavridi E. S., Waterman J. L. F. and Halazonetis T. D. (1998) ATM-dependent activation of p53 involves dephosphorylation and association with 14-3-3 proteins. Nat. Genet. **19:** 175–178
154 Hall J. and Angéle S. (1999) Radiation, DNA damage and cancer. Mol. Med. Today **5:** 157–164
155 Rotman G. and Shiloh Y. (1998) ATM: from gene to function. Hum. Mol. Genet. **7:** 1555–1563
156 Ivanov E. L. and Haber J. E. (1997) DNA repair: RAD alert. Curr. Biol. **7:** R492–R495
157 Varon R., Vissinga C., Platzer M., Cerosaletti K., Chrzanowska K., Saar K. et al. (1998) Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. Cell **93:** 467–476
158 Matsuura S., Tauchi H., Nakamura A., Kondo N., Sakamoto S., Endo S. et al. (1998) Positional cloning of the gene for Nijmegen breakage syndrome. Nat. Genet. **19:** 179–181
159 Featherstone C. and Jackson S. P. (1998) DNA repair: the Nijmegen breakage syndrome protein. Curr. Biol. **8:** R622–R625
160 Hofmann K. and Bucher P. (1995) The FHA domain: a putative nuclear signalling domain found in protein kinases and transcription factors. Trends Biochem. Sci. **20:** 347–349
161 Bork P., Hofmann K., Bucher P., Neuwald A. F., Altschul S. F. and Koonin E. V. (1997) A superfamily of conserved domains in DNA damage-responsive cell cycle checkpoint proteins. FASEB J. **11:** 68–76
162 Carney J. P., Maser R. A., Olivares H., Davis E. M., Le Beau M., Yates J. R. et al. (1998) The hMre11/hRad50 protein complex and Nijmegen breakage syndrome: linkage of double-strand break repair to the cellular DNA damage response. Cell **93:** 477–486
163 Rahman N. and Stratton M. R. (1998) The genetics of breast cancer susceptibility. Annu. Rev. Genet. **32:** 95–121
164 Ford D., Easton D. F., Bishop D. T., Narod S. A. and Goldgar D. E. (1994) Risks of cancer in BRCA1-mutation carriers: breast cancer linkage consortium. Lancet **343:** 692–695
165 Peto J., Collins N., Barfoot R., Seal S., Warren W., Rahman N. et al. (1999) Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J. Natl. Cancer Inst. **91:** 943–949
166 Soulier J. and Lowndes N. F. (1999) The BRCT domain of the *S. cerevisiae* checkpoint protein Rad9 mediates a Rad9-Rad9 interaction after DNA damage. Curr. Biol. **9:** 551–554
167 Sharan S. K., Morimatsu M., Albrecht U., Lim D.-S., Regel E., Dinh C. et al. (1997) Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking *Brca2*. Nature **386:** 804–810
168 Scully R., Chen J., Plug A., Xiao Y., Weaver D., Feunteun J. et al. (1997) Association of BRCA1 with Rad51 in mitotic and meiotic cells. Cell **88:** 265–275
169 Scully R., Chen J., Ochs R. L., Keegan K., Hoekstra M., Feunteun J. et al. (1997) Dynamic changes of BRCA1 subnuclear localisation and phosphorylation state are initiated by DNA damage. Cell **90:** 425–435
170 Thomas J., Smith M., Tonkinson J., Rubinfeld B. and Polakis P. (1997) Induction of phosphorylation on BRCA1 during the cell cycle and after DNA damage. Cell Growth Differ. **8:** 801–809
171 Patel K. J., Yu C. P. C. C., Lee H., Corcoran A., Thistlewaite F. C., Evans M. J. et al. (1998) Involvement of Brca2 in DNA repair. Mol. Cell **1:** 347–357
172 Connor F., Bertwistle D., Mee P. J., Ross G. M., Swift S., Grigorieva E. et al. (1997) Tumorigenesis and a DNA repair defect in mice with a truncating *Brca2* mutation. Nat. Genet. **17:** 423–430
173 Bertwistle D. and Ashworth A. (1998) Functions of the BRCA1 and BRCA2 genes. Curr. Opin. Genet. Dev. **8:** 14–20
174 Fan S., Wang J.-A., Yuan R., Ma Y., Meng Q., Erdos M. R. et al. (1999) BRCA1 inhibition of estrogen receptor signaling in transfected cells. Science **284:** 1354–1356
175 Milner J., Ponder B., Hughes-Davies L., Seltmann M. and Kouzarides T. (1997) Transcriptional activation functions in BRCA2. Nature **386:** 772–773
176 Harkin D. P., Bean J. M., Miklos D., Song Y.-H., Truong V. B., Englert C. et al. (1999) Induction of *GADD45* and JNK/SAPK-dependent apoptosis following inducible expression of BRCA1. Cell **97:** 575–586
177 Somasundaram K., Zhang H., Zeng Y.-X., Houvras Y., Peng T., Zhang H. et al. (1997) Arrest of the cell cycle by the tumor-suppressor BRCA1 requires the CDK-inhibitor $p21^{WAF1/CIP1}$. Nature **389:** 187–190
178 Chapelle A. de la and Peltomäki P. (1998) The genetics of hereditary common cancers. Curr. Opin. Genet. Dev. **8:** 298–303
179 Modrich P. and Lahue R. (1996) Mismatch repair in replication fidelity, genetic recombination, and cancer biology. Annu. Rev. Biochem. **65:** 101–133
180 Aarnio M., Sankila R., Pukkala E., Salovaara R., Aaltonen L., Chapelle A. de la et al. (1999) Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int. J. Cancer **81:** 214–218
181 Akiyama Y., Sato H., Yamada T., Nagasaki H., Tsuchia A., Abe R. et al. (1997) Germ-line mutation of the hMSH6/GTBP gene in an atypical hereditary nonpolyposis colorectal cancer kindred. Cancer Res. **57:** 3920–3923
182 Miyaki M., Konishi M., Tanaka K., Kikuchi-Yanoshita R., Muraoka M., Yasuno M. et al. (1997) Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. Nat. Genet. **17:** 271–272

183 Souza R. F., Appel R., Yin J., Wang S., Smolinski K. N., Abraham J. M. et al. (1996) Microsatellite instability in the insulin-like growth factor II receptor gene in gastrointestinal tumours. Nat. Genet. **14:** 255–257
184 Souza R. F., Kin J., Smolinski K. N., Zou T.-T., Wang S., Shi Y.-Q. et al. (1997) Frequent mutation of the *E2F-4* cell cycle gene in primary human gastrointestinal tumors. Cancer Res. **57:** 2350–2353
185 Rampino N., Yamamoto H., Ionov Y., Li Y., Sawai H., Reed J. C. et al. (1997) Somatic frameshift mutations in the *BAX* gene in colon cancers of the microsatellite mutator phenotype. Science **275:** 967–969
186 Abdel-Rahman W. M., Georgiades I. B., Curtis L. J., Arends M. J. and Wyllie A. H. (1999) Role of *BAX* mutations in mismatch repair-deficient colorectal carcinogenesis. Oncogene **18:** 2139–2142
187 Myeroff L. L., Parsons R., Kim S.-J., Hedrick L., Cho K. R., Orth K. et al. (1995) A transforming growth factor β receptor type II gene mutation common in colon and gastric but rare in endometrial cancers with microsatellite instability. Cancer Res. **55:** 5545–5547
188 Wicking C., Simms L. A., Evans T., Walsh M., Chawengsaksophak K., Beck F. et al. (1998) CDX2, a human homologue of *Drosphila caudal*, is mutated in both alleles in a replication error positive colorectal cancer. Oncogene **17:** 657–659