Genetic Predisposition and Genetic Susceptibility

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6.1 Introduction

More attention has been paid to the inherited nature of malignant tumors in children and adolescents, lately. Children with rare tumors may be at an increased risk of cancer because of a known cancer predisposition syndrome as Li-Fraumeni syndrome in case of adrenocortical tumors or multiple endocrine neoplasia (MEN2) in case of medullary thyroid tumors. Such cancer syndromes are commonly suspected in case of multiple malignancies within a family or a patient himself and/or in case of an adult-type tumor in children or adolescents. Interestingly though, it could be shown that strong predisposing mutations like BRCA1 and BRCA2, leading to individual risks of breast cancer of around 60% by age 70, together account for less than 5% of overall breast cancer incidence (Ponder 2001). Also, pediatric oncologists are not trained to pick up minor signs of cancer susceptibility, and therefore, syndromes might be overlooked. As discussed further down, it could be shown that the prevalence of minor and major morphological abnormalities is higher in patients with childhood cancers compared with controls – once more stressing the importance of constitutional genetic defects in pediatric oncogenesis and maybe pointing to so far unknown predisposition syndromes (Merks et al. 2008). This article gives an overview of mechanisms leading to cancer susceptibility, of known cancer syndromes (Table 6.1), and of the diagnostic approach and management, which can be followed in case of a suspected genetic predisposition for cancer. Within the single chapters of this book discussing the etiology of specific rare entities, several cancer syndromes are mentioned. Please refer to these chapters for detailed information on specific cancer syndromes and related malignancies.

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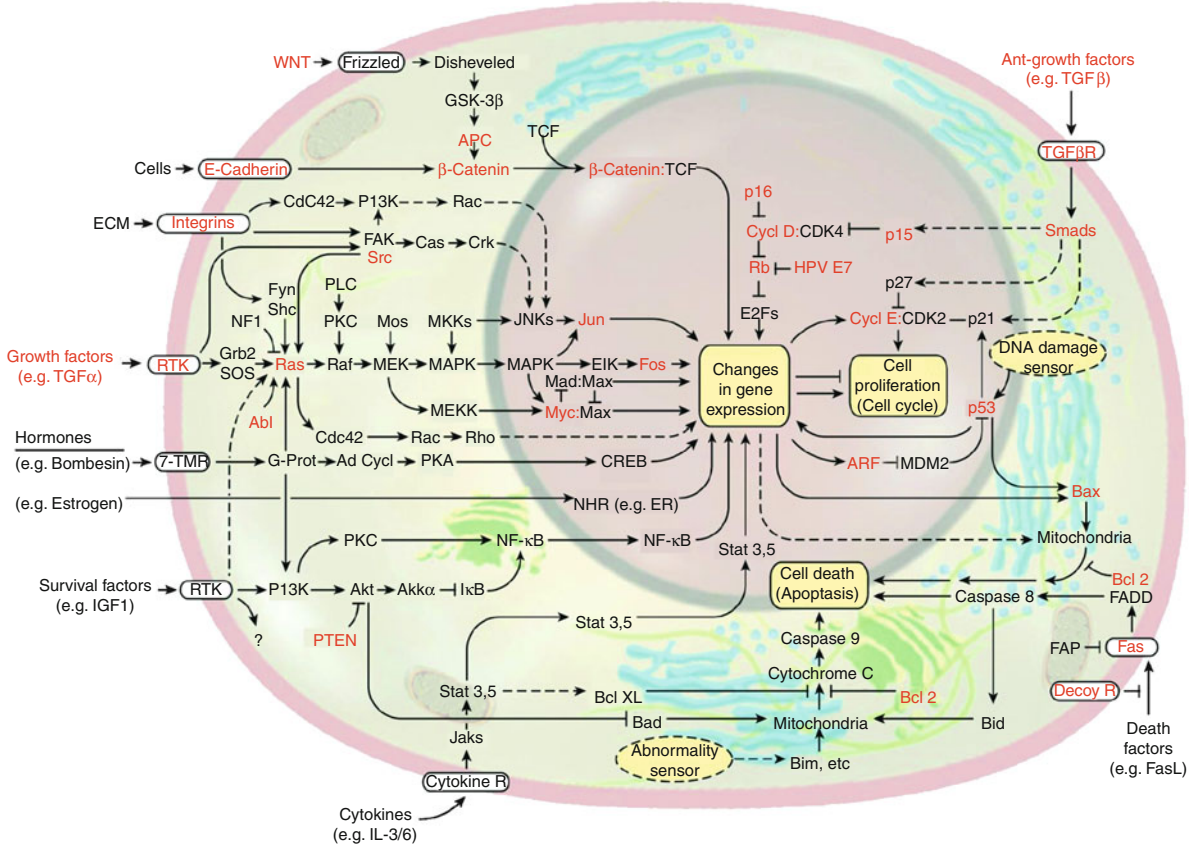

Fig. 6.1 The emergent integrated circuit of the cell (Courtesy of Hanahan and Weinberg 2000, with permission from Elsevier)

6.2 Hallmarks of Cancer Cells

Each cancer has traveled a specific route to arrive at its full phenotype. However, this multistep process can be reduced to a specific spectrum of acquired dysregulated cellular properties. Hanahan and Weinberg (2000) identified six 'hallmark characteristics' of the cancer cell phenotype:

1. *Self-sufficiency in growth signals:* Normal cells depend on mitogenic growth signals before they can enter a proliferative phase. Growth signals are transmitted to the cell via transmembrane receptors, binding three classes of signaling molecules: diffusible growth factors, extracellular matrix (ECM) components, and cell-to-cell adhesion/interaction molecules. Self-sufficiency in growth signals can be achieved by three mechanisms: (a) autocrine stimulation, i.e., cells producing their own growth factors; (b) transmembrane receptors abnormalities, such as overexpression of receptors (making the cell hyperresponsive to normal levels of growth factors), structural alterations of receptors leading to ligand independent signaling, or changes in the type of expressed ECM receptors (integrins), favoring pro-growth signals; and (c) alterations of the intracellular signaling circuit, e.g., the SOS-Ras-Raf-MAP kinase pathway playing a central role in signaling downstream of receptor tyrosine kinases (RTKs; binding diffusible growth factors) and integrins (Fig. 6.1, Hanahan and Weinberg 2000).
2. *Insensitivity to antigrowth signals:* Antigrowth signals are essential to block a cell from entering from the G1 into the S phase by inducing a quiescent (G0) state or postmitotic differentiation. Similar to growth factor signaling, antigrowth factors (soluble factors and immobilized factors embedded in the ECM) have their effect via binding to specific transmembrane receptors, inducing an intracellular signaling cascade. The intranuclear retinoblastoma protein (Rb-protein) has a central role here; in a hypophosphorylated state, Rb-protein binds to and inactivates the E2F transcription factors that control the expression of groups of genes essential for progression from G1 into S phase, blocking the cell from progression to the S phase (Weinberg 1995) (Fig. 6.1).

Normal cells are responsive to soluble antigrowth signals such as TGF-β that binds to its receptor (TGF-βR), signaling successively downstream via Smad4, p15 (INK4B), the CyclinD-CDK4 complex, eventually keeping the Rb-protein in a hypophosphorylated state (Fig. 6.1), thus blocking cell progression to a proliferative state. Disruption of the several steps of this pathway may result in insufficient response to antigrowth signals, making the cell insensitive to physiological growth inhibitory factors.

3. *Evading apoptosis:* Sensors and effectors constitute a complex circuit monitoring the intra- and extracellular environment for (ab)normalities and determining whether the cell should live or enter a phase of programmed cell death. Extracellular survival signals (e.g., IGF-1, IGF-2, and IL-3) and death signals (e.g., Fas ligand and TNFα) bind to their corresponding receptors (Fig. 6.1). Together with intracellular sensor signals, many converge on the mitochondria via different (often interacting) pathways such as the PI3–AKT pathway, members of the Bcl-2 family of proteins, and p53. When pro-apoptotic signals predominate, mitochondria release cytochrome C, catalyzing apoptosis. The ultimate effectors of apoptosis are a family of proteases, termed caspases, finally executing the death program (Fig. 6.1). Alterations in the several steps of this complex network, either potentiating the inhibitors of apoptosis (e.g., the upregulation of the Bcl-2 oncogene in lymphoma (Korsmeyer 1992)) or restraining the physiological death signals or apoptosis effectors (e.g., the epigenetic silencing of caspase 8 in neuroblastoma (Teitz et al. 2000)), withdraw the cell from its physiological "health security system."
4. *Limitless replicative potential:* Each cell seems to have a "counting device" for cell generations, called telomeres; the ends of chromosomes are composed of thousands of repeats of a short 6-base pair sequence element. Each cell replication leads to loss of 50–100 base pairs of the telomeric DNA of both ends of each chromosome. Multiple replications will lead to progressive shortening of the telomere ends, finally disabling the protective function of the telomeres after 60–70 replications (in cultured cells). This then leads to end-to-end chromosomal fusions, finally resulting in the death of the affected cell (Hayflick 1997). Telomere maintenance is a capacity virtually all cancers have obtained, either by upregulating expression of the telomerase enzyme (which adds hexanucleotide repeats onto telomeric ends) or by activating ALT, which maintains telomeres through recombination-based interchromosomal exchanges of sequence information.
5. *Sustained angiogenesis:* Like normal cells, tumor cells depend on nutrients and oxygen, obliging them to reside within 100 μm of a capillary. In a physiological state, proliferating cells are unable to induce angiogenesis. Tumor progression requires the neoplastic cells to gain angiogenic ability. Many tumors show increased expression of soluble growth factors like VEGF and FGF, both binding to their corresponding transmembrane tyrosine kinase receptors on endothelial cells. On the other hand, endogenous angiogenesis inhibitors, such as thrombospondin-1 or β-interferon, may be downregulated. Integrins and adhesion molecules, respectively mediating cell-matrix and cell-cell adhesion, play crucial roles in the regulation of angiogenesis. Proteases in the ECM can control the bioavailability of angiogenic activators and inhibitors. Disturbances at the different levels of the "angiogenic switch" may result in a sustained pro-angiogenic state.
6. *Tissue invasion and metastasis:* Cadherins, cell adhesion molecules (CAMs) (Cavallaro and Christofori 2004), integrins, and proteases (Fig. 6.1) play key roles in the ability of cancer cells to become invasive or metastatic. Normal epithelial cells show intercellular E-cadherin bridges with their neighbors, resulting in antigrowth signals via β-catenin. In most epithelial cancers this pathway is disrupted. Changes in the isoform of the cell adhesion molecule N-CAM, from a highly adhesive to a poorly adhesive or even repulsive isoform, and reductions in overall expression of the N-CAM molecule will lead to reduced cell-cell adhesion, favoring the metastatic capacity of tumor cells. Alterations of integrin expression enable the adaptation of tumor cells to a changing microenvironment in their invasive and metastatic journeys. Finally, upregulation of protease genes and downregulation of protease inhibitor genes will enable the docking of active proteases on the cancer cell surface, facilitating invasion of cancer cells into nearby structures.

6.3 Acquisition of Tumorigenic Alterations

Apparent from the six hallmarks, for a cell to become a cancer cell, multiple (epi)genetic changes have to occur to establish conflict with maintenance of

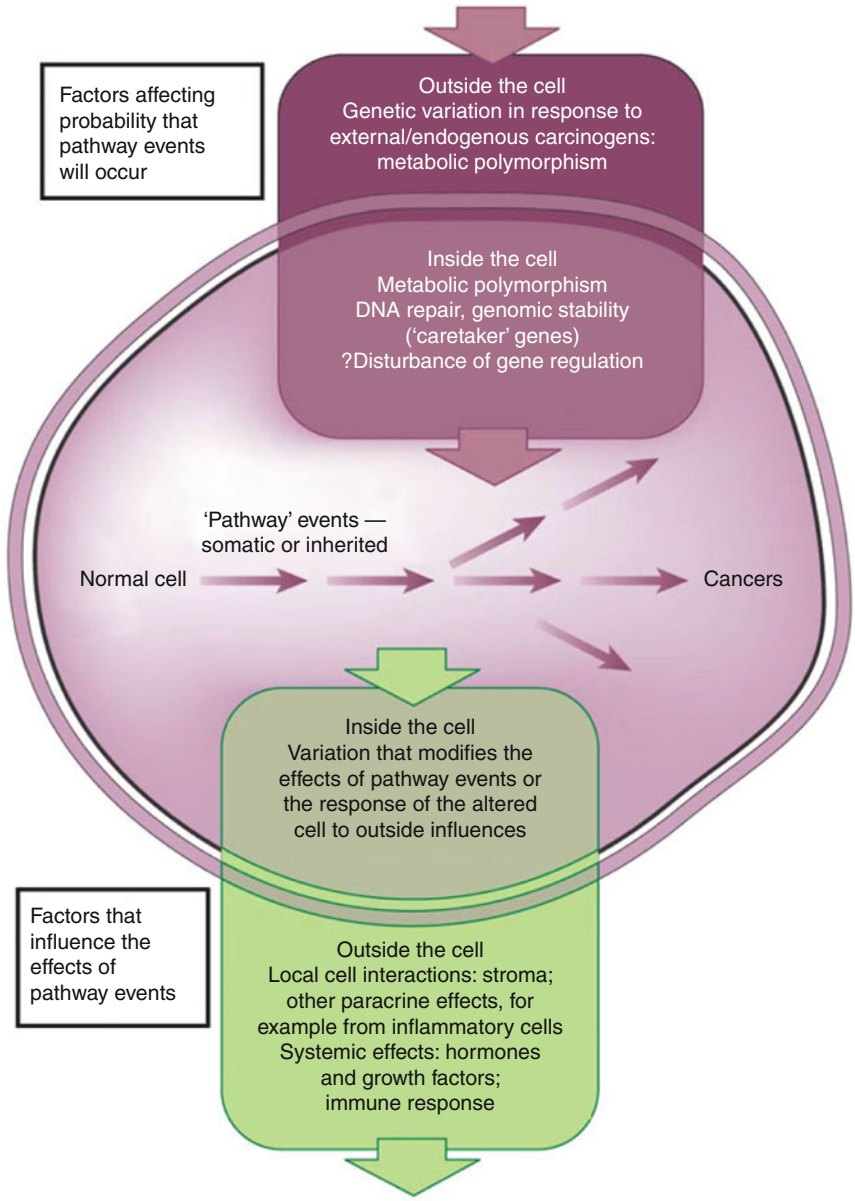

Fig. 6.2 A framework for genetic effects on cancer development (Courtesy of Bruce Ponder 2001, with permission from Nature Publishing Group). *Horizontal arrows* represent the successive pathway events giving the cell the full cancer phenotype. Many are somatic events, but in inherited cancer predisposition syndromes, one of the events is inherited. The diverging arrows on the right represent the variety of events that can lead to overtly similar cancers. *Vertical arrows* represent pathway event influencing factors

genomic integrity. Acquired or constitutive malfunction of genomic caretaker systems is often required to allow cells to take the multiple steps on the cancer ladder.

Host factors influencing the acquisition of tumorigenic alterations: The several steps in the evolution of a cancer are influenced by multiple factors from in and outside the cell (Fig. 6.2; Ponder 2001 and references therein (Ponder 2001)).

6.3.1 Factors Affecting the Probability that Tumorigenic Alterations Will Occur

External influences include environmental exposures, such as cigarette smoke, diet, or UV-light exposure, the response to which may be modified by genetic variation in intra- and extracellular metabolism (Peto 2001). For example, less than 20% of smokers develop lung cancer,

indicating that many host factors determine individual susceptibility, such as extent of carcinogen uptake, metabolic activation and detoxification, DNA repair ability, apoptosis and varying effects on genes in signal transduction pathways, and regulation of the cell cycle (Hecht 2002).

6.3.2 Factors that Influence the Effects of Tumorigenic Alterations

Variation of intracellular factors will modify the effect of a particular genetic pathway event on the cellular phenotype, or its response to signals from outside. Paracrine interactions with neighboring cells, systemic effects from circulating hormones or growth factors, and immunologic responses of the host comprise some of the external factors that modulate the effects of pathway events (Tlsty and Hein 2001; Dranoff 2004). Genetic variation of these factors probably accounts for much of the low-level predisposition to cancer, as it occurs in the "normal" population (Ponder 2001; Nadeau 2001).

6.4 Cancer Predisposition

Family history and clinical phenotype are the cardinal aspects of inherited tumor predisposition syndromes. In his review on cancer genetics, Ponder discerned strong and weak tumor predisposition (Ponder 2001). Paradoxically, the largest category of inherited tumor predisposition, in terms of its contribution to cancer incidence, is the one with the weakest genetic effects: tumor predisposition without evident family clustering, apparently caused by low-penetrance tumor predisposition genes. For example, in breast cancer, the strongly predisposing mutations in BRCA1 and BRCA2 lead to individual risks of around 60% by age 70. However, their combined contribution to overall breast cancer incidence is less than 5%. By contrast, a weak tumor predisposition gene, with a relative breast cancer risk of 2 and a population frequency of 20%, could account for up to 20% of breast cancer incidence (Ponder 2001).

Strong cancer predisposition: Strong tumor predisposition syndromes result from inheritance of either one of the events on the cancer pathway or a defective DNA repair system. Most syndromes show tissue specificity, although reasons for specific patterns of expression are mostly unclear. Another important characteristic is the variability of cancer incidence, and the type of cancers occurring within a given syndrome, but also within a single family. The within-syndrome variation can be accounted for by several factors: different germ line genes causing the same syndrome or different mutations in the same gene causing the same syndrome, genetic modifiers, environmental influences, or chance.

The within-family variation most probably is accounted for by the effects of genetic modifiers (Ponder 2001).

Weak cancer predisposition: Weak predisposition may result from weak alleles of the pathway or caretaker genes and from genetic variations of host factors influencing cancer development, as depicted in Fig. 6.2. These genes might be collectively called low-penetrance tumor predisposing genes. As described above, the word "weak" is misleading: Low-penetrance genes are thought to account for a relatively large part of cancer incidence, and studying them may provide much information about many different cancers, with important potential public health implications.

6.5 Syndromes and Childhood Cancer

Cancer syndromes account for approximately 5–10% of all cancers in adulthood. Our understanding of familial cancer syndromes is increasing rapidly, with the emphasis shifting towards early detection of at-risk families. Anyway, so far, not much is known about the exact risk of children to be affected of malignant tumors in case of a cancer syndrome, and specific prevention programs are to be established.

To establish the incidence and spectrum of malformation syndromes associated with childhood cancer, Merks et al. (2005a) performed a clinical morphological examination on a series of 1,073 children with cancer. A syndrome was diagnosed in 42 patients (3.9%) and the presence of a syndrome suspected in another 35 patients (3.3%), for a total of 7.2%. Twenty of the 42 syndrome diagnoses were not recognized in the patients prior to this study, indicating that these diagnoses are commonly missed. Therefore, all children with a malignancy should be examined by a clinical geneticist or a pediatrician skilled in clinical morphology. Besides the known syndromes, new tumor predisposition syndromes can be recognized as a result of such a meticulous clinical genetic evaluation of a large cohort of childhood cancer patients (Merks et al. 2008).

An overview of syndromes with concurring tumors in childhood is presented in Table 6.1. Most tumor syndromes in childhood are listed, together with main references and a summary of their (presumed)

Table 6.1 Childhood tumor predisposition syndromes

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Aase–Smith I (Patton et al. 1985)	AD	Unknown	Unknown	Unknown	Brain, palate, joints	Neuroblastoma	Concurrence
Acanthosis nigricans (Curth et al. 1962)	Neoplasia related	Unknown	Unknown	EpidermalGF (Douglas et al. 1994) FibroblastGF (Meyers et al. 1995)	Mouth, skin	Abdominal adenocarcinoma (60% stomach)	Tumor predisposition
Ataxia telangiectasia (Boder 1975)	AR	11q22.3	*ATM*	ATM encodes a protein similar to phosphoinositol 3-kinases, involved in mitogenic signal transduction, meiotic recombination, and cell cycle control; ATM kinase activates c-Abl tyrosine kinase in the cellular response to ionizing radiation (Baskaran et al. 1997)	Face, brain, eyes, immune system, skin	Non-Hodgkin lymphoma, acute lymphoblastic leukemia, Hodgkin disease, carcinoma (medulloblastoma, adenocarcinoma of stomach, glioma, carcinoma of skin, gallbladder, liver, larynx, thyroid, ovary, breast, and parotid gland)	Tumor predisposition
Bannayan–Riley–Ruvalcaba (Gorlin et al. 1992)	AD	10q23	*PTEN*	Tumor suppressor encoding a dual specificity phosphatase: 1. lipid phosphatase – PI3K/AKT 2. protein phosphatase – MAPK (Waite and Eng 2002)	Craniofacial, thyroid, GI-tract, musculoskeletal, skin	Lipoma, vascular malformation, hamartomas, intestinal polyposis (breast cancer, follicular thyroid cancer, endometrial carcinoma)	Tumor predisposition
Bazex–Dupré–Christol (Goeteyn et al. 1994)	X-linked dominant	Xq24-q27	Unknown	Unknown	Nose, skin	Basal cell carcinoma	Tumor predisposition
Beckwith–Wiedemann/ Wiedemann–Beckwith (Choufani et al. 2010)	Variable: cytogenetic/ gene defect/ imprinting disturbance	11p15	*IGF2, KCNQ1OT1, H19, CDKN1C*	Deregulation of imprinted genes found in 2 domains within the 11p15 region: – *IGF2* and KCNQ1OT1 (=*LIT1/KvDMR1)*: growth promoters (IGF2: autocrine growth factor; mediator of growth hormone action, stimulator of the action of insulin) – *H19* and CDKN1C (encodes the $p57^{KIP2}$ protein: tumor suppressor (Engel et al. 2000)	Overgrowth, tongue, ear, abdomen	Wilms' tumor, hepatoblastoma, adrenocortical carcinoma (hepatocellular carcinoma, neuroblastoma, glioblastoma, rhabdomyosarcoma, lymphoma, pancreaticoblastoma, renal cell carcinoma, myelodysplasia, yolk sac tumor, intratubular germ cell neoplasm, teratoma, carcinoid tumor, fibroadenoma, fibrous hamartoma, ganglioneuroma, adrenal cortex adenoma myxoma, cardiac hamartoma)	Tumor predisposition

Bloom (German 1993)	AR	15q26.1	RECQL3	Member of RecQ family helicases, maintenance of DNA integrity (Ellis and German 1996)	Growth, immune system, genitalia, skin	Acute lymphocytic leukemia, acute myeloid leukema, non-Hodgkin lymphoma, adenocarcinoma, squamous cell carcinoma (Wilms' tumor, medulloblastoma, osteosarcoma, Hodgkin lymphoma)	Tumor predisposition
Breast (and ovarian) cancer (Carter 2001)	AD	17q21 13q12.3	*BRCA1* *BRCA2*	Tumor suppressor genes; involved in maintenance of genomic integrity, at least in part by cooperating with recombinational repair proteins (Scully 2000)	Breast, ovary Breast, prostate, pancreas	(Breast cancer, ovarian cancer) (Breast cancer, pancreatic, prostate cancer)	Tumor predisposition
Carney type I (Carney 1995) Carney type II	AD 50% de novo	17q23-q24 2p16	*PRKAR1A* *Unknown*	Tumor suppressor gene, phosphorylation of many substrates including transcription factor CREB (Montminy 1997) Unknown	Eyes, heart, breast, GU-tract, endocrine system, skin	Myxomas (heart, skin, breast), pituitary tumors, adrenal cortical rest tumor, thyroid tumors, pheochromocytoma, Leydig cell tumor, large-cell calcifying Sertoli cell tumor of testis, schwannomas, myxoid breast fibroadenoma and ductal adenoma	Tumor predisposition
Cartilage-hair hypoplasia (Makitie et al. 1995)	AR	9p21-p12	RMRP	Processing of ribosomal RNA (Ridanpaa et al. 2001)	Hair, skeleton, immune system	Hodgkin disease, non-Hodgkin lymphoma, skin, eye, and liver cancer, leukemia, testicular tumor, basal cell carcinoma	Tumor predisposition
Cardio-facio-cutaneous (Armour and Allanson 2008)	sporadic	7q34 15q21 19p13.3	*BRAF, MEK1, MEK2*	*RAS/MAPK pathway*: Regulation of cell growth, differentiation, proliferation, and apoptosis *BRAF* is a proto-oncogene (Niihori et al. 2006)	Growth, craniofacial, brain, eyes, chest, heart, skin	Acute lymphoblastic leukemia, hepatoblastoma	Concurrence
Costello (Hennekam 2003)	AD	11p15.5	HRAS	Proto-oncogene; encodes signal transduction molecules (Aoki et al. 2005)	Craniofacial, brain, heart, musculoskeletal, skin	Rhabdomyosarcoma, (ganglio)neuroblastoma (bladder carcinoma, acoustic neurinoma, epithelioma)	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Cowden (Pilarski and Eng 2004)	AD	10q23	*PTEN*	Tumor suppressor encoding a dual specificity phosphatase: 1. lipid phosphatase – PI3K/AKT 2. protein phosphatase – MAPK (Waite and Eng 2002)	Craniofacial, brain, thyroid, breasts, GU-tract, GI-tract, musculoskeletal, mucocutaneous	Angiolipoma, lipoma, vascular malformations, fibroma, trichilemmoma, intestinal polyposis (breast cancer, follicular thyroid cancer, dysplastic cerebellar gangliocytoma, endometrial carcinoma, renal cell carcinoma, colon carcinoma, meningioma, medulloblastoma, parotid hamartoma, neurofibroma, granular cell tumor, salivary gland carcinoma, liopsarcoma, acute myeloid leukemia, non-Hodgkin lymphoma, melanoma, bladder carcinoma, Merkel cell carcinoma of the skin)	Tumor predisposition
Del(9p) (Huret et al. 1988)	Chromosomal	9p22 (Predeliction)	Unknown	Unknown	Craniofacial, brain, neck, chest, abdomen, limbs	Acute lymphoblastic leukemia, gonadoblastoma (in 46,XY sex reversal cases), lymphoma, melanoma	Concurrence
Del(13q) (Brown et al. 1993)	Chromosomal	13q31-13q33	Unknown	Unknown (regarding tumor predisposition: Rb tumor suppressor gene involved (Classon and Harlow 2002))	Craniofacial, brain, neck, heart, GU-tract, anus, limbs	Retinoblastoma, osteosarcoma, synovial sarcoma	Tumor predisposition
Denys–Drash (Mueller 1994)	Sporadic	11p13	WT1	Inactivation of tumor suppressor/transcription factor WT1 (Rauscher 1993)	GU-tract	Wilms' tumor (gonadoblastoma)	Tumor predisposition
Diethylstilbestrol embryopathy (Herbst et al. 1972)	Teratogen	–	–	–	GU-tract	Vaginal adenocarcinoma	Tumor predisposition
Down (Pueschel 1990)	Chromosomal	Trisomy 21	Entire chromosome 21	Overexpression of leukemogenic and solid tumor suppressor genes on chromosome 21 (Hasle et al. 2000)	Craniofacial, brain, thyroid, heart, abdomen, skeleton, skin	Acute myeloid leukemia, acute lymphoblastic leukemia *(germ cell tumor, lymphoma, retinoblastoma, pancreatic and bone tumors)*	Tumor predisposition

Dubowitz (Tsukahara and Opitz 1996)	AR	Unknown	Unknown	Unknown	Growth, craniofacial, brain, skin	Acute lymphoblastic leukemia, lymphoma, neuroblastoma , rhabdomyosarcoma, aplastic anemia	Concurrence
Dyskeratosis congenita (Sirinavin and Trowbridge 1975)	X-linked recessive	Xq28	*DKC1*	Dyskerin performs two functions: pseudouridylation and stabilization of the telomerase component of ribosomal RNA (Montanaro et al. 2006) Mutations impair telomerase maintenance, predisposing to malignancy, likely by impairing translation of tumor suppressor and antiapoptotic mRNA's	Growth, brain, eyes, ears, GI-tract, hematologic, immune system, mucocutaneous	Carcinomas of oral mucosa, nasopharynx, esophagus, stomach, rectum, cervix, and vagina; squamous cell carcinoma, adenocarcinoma of pancreas, Hodgkin disease	Tumor predisposition
Epidermal nevus/ Schimmelpenning (Goldberg et al. 1987)	Sporadic	Unknown	Unknown	Unknown	Brain, eye, skeleton, skin	Chondroblastoma, intrahepatic cyctic biliary adenomas, hemangioma, giant cell granuloma (other neoplasms may have been recorded in overlapping conditions)	Concurrence
Familial malignant melanoma (Greene 1997)	AD	9p21 12q14	*CDKN2A/p16* CDK4	Wildtype p16 arrests normal diploid cells in late G1 via inactivation of CyclinD-CDK4 complexes (Lukas et al. 1995) CyclinD-CDK4 complexes phosphorylate the Rb protein, hereby releasing the repression of E2F-mediated transcription, promoting progression through G1 (Classon and Harlow 2002)	Skin	Melanoma (pancreatic cancer) Melanoma	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Fanconi (Giampietro et al. 1993)	AR	16q24.3, Xp22.31, 9q22.3, 3p25.3, 6p21.3, 11p15, 9p13, 17q22-q24 2p16, 14q21.3, 13q12.3	*FANCA, FANCB, FANCC, FANCD2-FANCE, FANCF, FANCG, FANCJ, FANCL, FANCM,* FANCD1 (=biallelic BRCA2)	11 different FA genes encode for a complex web of interacting proteins that are involved in the recognition or repair of DNA interstrand crosslinks and perhaps other forms of DNA damage (Mathew 2006)	Heart, kidney, limb, hematologic, skin	Acute myeloid leukemia, myelodysplastic syndrome, hepatocellular adenoma and carcinoma, squamous cell carcinoma of head and neck, vulva and cervix medulloblastoma, Wilms' tumor, acute myeloid leukemia, acute lymphatic leukemia	Tumor predisposition
Fetal alcohol (Clarren and Smith 1978)	Teratogen	–	–	–	Growth, face, brain, heart, GU-tract, skin	(Ganglio)neuroblastoma, Wilms' tumor, germ cell tumors, hepatoblastoma, rhabdomyosarcoma, medulloblastoma, acute lymphoblastic leukemia, Hodgkin disease, adrenal carcinoma (Kiess et al. 1984)	Concurrence
Fetal hydantoin (Hanson 1986)	Teratogen	–	–	–	Growth, craniofacial, brain, neck, heart, abdomen, genitalia, limbs	Neuroblastoma, ependymoblastoma, ganglioneuroblastoma, melanotic neuroectodermal tumor of infancy, Hodgkin disease, mesenchymoma, Wilms tumor	Concurrence
Frasier (Moorthy et al. 1987)	Sporadic	11p13	WT1	Inactivation of tumor suppressor/transcription factor WT1 (Klamt et al. 1998)	GU-tract	Gonadoblastoma (Wilms')	Tumor predisposition

Gardner/familial adenomatous polyposis (Cohen 1982)	AD	5q21	*APC*	Tumor suppressor, mutations leading to stabilization of β-catenin in the WNT/β-catenin pathway, activating TCF transcription factors (Fearnhead et al. 2001)	Eyes, teeth, skeleton, GI-tract, abdomen skin	Osteoma, polyposis, colon cancer, desmoid tumors, glioma, medulloblastoma, papillary thyroid carcinoma (adrenal adenoma, adrenal adenocarcinoma, hepatocellular carcinoma, hepatoblastoma, retroperitoneal leiomyoma, neurofibroma, rhabdomyosarcoma, osteosarcoma, osteochondroma, chondrosarcoma, lipoma, fibroma of the breast, basal cell carcinoma)	Tumor predisposition
Glycogen storage disease I (Hirschhorn 2001)	AR	17q21	*G6PC*	Unknown (Limmer et al. 1988)	Growth, face, liver, kidney, musculoskeletal, skin	Liver adenomas, hepatocellular carcinomas	Tumor predisposition
Gorlin (nevoid basal cell carcinoma) (Gorlin 1987)	AD 35–50% de novo	9q22.3	*PTCH1*	Inactivation of tumor suppressor/SHH-PTCH1-SMO-GLI pathway (Villavicencio et al. 2000)	Craniofacial, brain, eyes, heart, GI-tract, ovaries, skeleton, skin	Basal cell carcinoma, medulloblastoma, cardiac fibroma, mesenteric cysts, ovarian fibroma and fibrosarcoma, rhabdomyoma, rhabdomyosarcoma, leiomyoma, leiomyosarcoma, lymphangiomyoma, melanoma, mesenchymoma, Hodgkin lymphoma, seminoma, schwannoma, pleiomorph adenoma of parotid, adrenal cortical adenoma	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Hemihyperplasia (Cohen 1989)	Sporadic	Unknown Partly 11p15	Unknown *IGF2, KCNQ1OT1, H19, , CDKN1C*	Unknown Deregulation of imprinted genes found in 2 domains within the 11p15 region: – IGF2 and KCNQ1OT1 (=LIT1/KvDMR1): growth promoters (IGF2: autocrine growth factor; mediator of growth hormone action, stimulator of the action of insulin) – *H19* and CDKN1C (encodes the $p57^{KIP2}$ protein: tumor suppressor (Bliek et al. 2008)	Overgrowth, face, breast, limbs	Wilms' tumor, hepatoblastoma, adrenocortical carcinoma (neuroblastoma, pheochromocytoma, testicular carcinoma, undifferentiated sarcoma)	Tumor predisposition
Hereditary leiomyomatosis and renal cell cancer (Tomlinson et al. 2002)	AD	1q42.1	*FH*	Fumarate hydratase is an enzyme of the tricarboxylic acid cycle; the mechanism leading to tumor predisposition remains unclear (Tomlinson et al. 2002)	Kidney, GU-tract, skin	(Leiomyomata of skin and uterus, renal cell carcinoma)	Tumor predisposition
Hereditary papillary renal cell carcinoma (Zbar et al. 1995)	AD	7q31	*MET*	Proto-oncogene encoding a transmembrane receptor kinase (Schmidt et al. 1997)	Kidney	(Papillary renal cell carcinoma)	Tumor predisposition
Hereditary paraganglioma and pheochromocytoma (Baysal 2002)	AD	11q23 1q21 1p36.1-p35	*SDHD* *SDHC* *SDHB*	Encoding subunits of the mitochondrial complex II; mutations possibly leading to dysregulation of hypoxia-responsive genes and impairment of mitochondria-mediated apoptosis (Maher and Eng 2002)	Adrenal glands, extra-adrenal paraganglion tissue	(Paraganglioma, pheochromocytoma)	Tumor predisposition

Hereditary non-polyposis colorectal cancer (Lynch syndrome) (Vasen et al. 1999)	AD	2p22-21 2p16 3p21 2q31-33 7p22 *Biallelic mutation carriers of:* 2p22-21 2p16 3p21 7p22	*MSH2* *MSH6* *MLH1* *PMS1* *PMS2* *MSH2* *MSH6* *MLH1* *PMS2*	DNA-mismatch repair (Lynch and de La 1999)	Breast, GI-tract, GU-tract, skin	(Colorectal and endometrial carcinoma) (Other GI and GU-tract carcinomas, skin carcinoma, breast cancer, and leukemia) Childhood primary brain malignancies, hematological malignancies, and	Tumor predisposition
Hyperparathyroidism, jaw fibroma (Inoue et al. 1995)	AD	1q25-q31	*HRPT2*	Inactivation of tumor suppressor encoding for parafibromin (Carpten et al. 2002)	Jaws, parathyroid glands	Parathyroid adenoma and carcinoma, multiple ossifying fibromas, Wilms' tumor	Tumor predisposition
Incontinentia pigmenti (Landy and Donnai 1993)	X-linked dominant	Xq28	*NEMO*	Activation of transcription factor NF-kappaB (central to many immune, inflammatory, and apoptotic pathways) (Smahi et al. 2000)	Eyes, teeth brain, skin	Retinoblastoma, Wilms' tumor, acute myeloid leukemia, rhabdomyosarcoma	Tumor predisposition
Juvenile polyposis coli (Veale et al. 1966)	AD	18q21.1 10q22.3	*SMAD4/ DPC4* *BMPR1A*	Inactivation of tumor suppressor and central mediator of Smad function in TGF-β signaling pathway (Zhang et al. 1997) Type I receptor in TGF-β/ BMP signaling (Howe et al. 2001)	GI-tract	Gastrointestinal hamartomatous polyps, GI- cancer	Tumor predisposition
Leukoplakia, tylosis, and esophageal carcinoma (Tyldesley and Hughes 1973)	AD	17q25	*EVPL*	Membrane-associated precursor of the epidermal cornified envelope, considered to link desmosomes and keratine filaments to the cornified envelope (Ruhrberg et al. 1996)	GI-tract, mucocutaneous	Leukoplakia (esophageal cancer)	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Li-Fraumeni syndrome (Li et al. 1988)	AD	17p13.1	TP53	Inactivation of tumor suppressor regulating several downstream genes: p21 and MDM-2 (cell cycle control), Gadd45 (repair) and Bax and IGF-BP (apoptosis) (Levine 1997)	Ubiquitous	Rhabdomyosarcoma, soft tissue sarcomas, brain cancer, bone sarcomas (with the exception of Ewing sarcoma), adreno-cortical tumors, leukemia, lymphoma (neuroblastoma, Wilms tumor, lung cancer, GI-cancer, endometrial cancer, squamous cell carcinoma, melanoma, breast cancer, ovary cancer, prostate cancer, thyroid cancer)	Tumor predisposition
Maffucci (Lewis and Ketcham 1973)	Sporadic	Unknown	Unknown	Unknown	Skeleton, vascular system	Vascular malformations, enchondroma, chondrosar-coma (olfactory neuroblas-toma, angiosarcoma, ovary tumors, brain tumors, pancreatic carcinoma, hepatic adenocarcinoma, pituitary adenoma)	Tumor predisposition
McCune–Albright (Danon and Crawford 1987)	Somatic mosaicism Usually sporadic	20q13.2	*GNAS1*	Activation of the stimulatory Gsα protein; Gsα protein couples receptors causing activation of adenylate cyclase, thereby increasing cAMP synthesis (Weinstein et al. 1991; Cohen and Howell 1999)	Endocrine system, skeleton, skin	Osteosarcoma, intramuscu-lar myxoma, leukemia, meningioma (breast cancer, endometrial carcinoma)	Concurrence
Mulibrey nanism (Karlberg et al. 2004)	AR	17q22-q23	*TRIM37*	Encoding a RING-B-box-coiled-coil protein of unknown function, localized in the peroxisomes (Kallijarvi et al. 2002)	Growth, face, eyes, mouth, brain, heart, liver, musculoskeletal, skin	Wilms' tumor	Tumor predisposition

Multiple endocrine neoplasia type 1 (Thakker 1998)	AD	11q13	*MEN1*	Inactivation of tumor suppressor encoding the protein menin; menin binds directly to JunD and inhibits JunD-activated transcription (Agarwal et al. 2004)	Endocrine system	(Tumors of the parathyroids, pancreatic islet cells, and anterior pituitary) (Adrenal cortical tumors, carcinoid, lipoma, angiofibroma, collagenoma)	Tumor predisposition
Multiple endocrine neoplasia type 2A (Brandi et al. 2001)	AD	10q11.2	*RET*	Proto-oncogene encoding a receptor tyrosine kinase, signaling through several pathways, including RAS/ERK, MAPK, NFκB, P13/AKT, and JNK, thus driving cell proliferation, survival, migration, or differentiation (Takahashi 2001)	Endocrine system, skin, GI-tract	Pheochromocytoma, medullary thyroid carcinoma, parathyroid adenoma	Tumor predisposition
Multiple endocrine neoplasia type 2B (Morrison and Nevin 1996)	AD 50% de novo	10q11.2	RET	See MEN 2A; 2 different MEN 2B specific mutations: 96% M918T 4% A883F (Eng et al. 1996)	Face, eyes, larynx, thyroid, adrenal gland, GI-tract, musculoskeletal	Pheochromocytoma, medullary thyroid carcinoma, mucosal neuroma	Tumor predisposition
Neurofibromatosis type I (Viskochil 1999)	AD 50% de novo	17q11.2	*NF1*	Inactivation of tumor suppressor/loss of inhibition of Ras oncogene activity (Cichowski and Jacks 2001)	Craniofacial, eyes, brain, vascular system, skeleton, skin	Neurofibroma, plexiform neurofibroma, optic glioma, schwannoma, meningioma, astrocytoma, medulloblastoma, ependymoma, neurofibrosarcoma, malignant peripheral nerve sheath tumor (rhabdomyosarcoma, neuroblastoma, Wilms tumor, juvenile myelomonocytic leukemia, pheochromocytoma, adenosarcoma of pancreas, liposarcoma, melanoma)	Tumor predisposition
Neurofibromatosis type II (Evans et al. 2000)	AD	22q12.2	*NF2*	Inactivation of tumor suppressor/loss of merlin interaction with multiple proteins involved in cell-cell and cell-matrix signals (Gutmann 2001)	Eyes, brain, skin	Acoustic neuroma, neurofibroma, meningioma, glioma, schwannoma, ependymoma	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Nijmegen breakage (van der Burgt et al. 1996)	AR	8q21	*NBS1*	Mutated DNA double-strand break repair protein; Nbs1 potentiates ATP-driven DNA unwinding and endonuclease cleavage by the Mre11/Rad50 complex (Varon et al. 1998; Paull and Gellert 1999)	Growth, craniofacial, immune system	Acute lymphoblastic leukemia, lymphoma, neuroblastoma, glioma, medulloblastoma, rhabdomyosarcoma	Tumor predisposition
Noonan (Allanson 1987)	AD 25–70% de novo	12q24.1	*PTPN11*	Gain of function in tyrosine phosphatase SHP2. SHP2 is involved in intracellular signaling downstream to several growth factor, cytokine, and hormone receptors. SHP2 stimulates the RAS/MAPK pathway (Fragale et al. 2004)	Growth, craniofacial, eyes, brain, heart, lymphatic system, abdomen, GU-tract, skeleton, skin	Juvenile myelomonocytic leukemia, neuroblastoma (acute lymphoblastic leukemia, chronic myelomonocytic leukemia, rhabdomyosarcoma, testicular carcinoma, pheochromocytoma, astrocytoma, hepatoblastoma, malignant peripheral nerve sheath tumor)	Tumor predisposition
Opitz trigonocephaly (Antley et al. 1981)	Uncertain	Unknown	Unknown	Unknown	Craniofacial, brain, neck, heart, genital, limbs, skin	(Medulloblastoma)	Concurrence
Peutz–Jeghers (Westerman et al. 1999)	AD	19p13.3	*STK11*	Inactivation of tumor suppressor gene by loss of protein kinase activity; *STK11* interacts with the chromatin remodeling protein BRG1 and with the cell cycle regulatory proteins LIP1 and WAF1 (Yoo et al. 2002)	GI-tract, GU-tract, mucocutaneous	Gastointestinal hamartomas, adenomas and adenocarcinomas, granulosa cell tumors, dysgerminoma, cystadenoma, cervical adenocarcinoma, sex cord tumor with annular tubules, large cell Sertoli cell tumor, breast carcinoma, pancreatic adenocarcinoma, bile duct carcinoma	Tumor predisposition
Proteus (Biesecker et al. 1999)	Somatic mosaicism	Up to 20% of cases: 10q23 (Zhou et al. 2001)	Up to 20% of cases: *PTEN*	Inactivation of tumor suppressor encoding a dual specificity phosphatase: 1. lipid phosphatase – PI3K/AKT 2. protein phosphatase – MAPK (Waite and Eng 2002)	Overgrowth, craniofacial, lung, kidney, vascular system, skeleton, skin	Vascular malformations, lipomas (ovarian cystadenoma, testicular tumors, meningiomas, monomorphic adenoma of parotid gland)	Tumor predisposition
		Remainder: 14q32.33	Remainder: AKT1				
	(Lindhurst et al. 2011)			Mosaic activation of AKT1 (Lindhurst et al. 2011)			

Retinoblastoma (hereditary) (Knudson et al. 1975)	AD 80% de novo	13q14.1-q14.2	*RB1*	Inactivation of tumor suppressor/repressor of E2F-mediated transcription, inhibiting progression through G1 (Classon and Harlow 2002)	Eyes	Retinoblastoma, osteosarcoma, pinealoma	Tumor predisposition
Ring-shaped skin creases, cleft palate (Cohen et al. 1993)	AD	Unknown	Unknown	Unknown	Craniofacial, skin	Neuroblastoma, smooth muscle hamartoma	Concurrence
Rothmund–Thomson (Wang et al. 2001a)	AR	8q24.3	*RECQL4*	Member of RecQ family helicases; maintenance of DNA integrity (Kitao et al. 1999)	Growth, craniofacial, eyes, endocrine system, limbs, skeleton, skin	Osteosarcoma, fibrosarcoma, squamous cell carcinoma (melanoma, gastric carcinoma)	Tumor predisposition
Rubinstein–Taybi (Rubinstein 1990)	AD >99% de novo	16p13.3	*CBP*	Haploinsufficiency of the transcriptional cofactor CBP, which is involved as downstream effector in many pathways, particularly the SHH-PTCH-GLI pathway (Petrij et al. 1995)	Growth, craniofacial, brain, GU-tract, limbs, skeleton	Rhabdomyosarcoma, neuroblastoma, pheochromocytoma, acute lymphoblastic leukemia, angioblastic meningioma, neurilemmoma, gonadal sex cord stromal cell tumor, hemangioendothelioma, acute leukemia	Tumor predisposition
Silver–Russell (Patton 1988)	Heterogeneous	Heterogeneous 11p15.5 Maternal disomy 7	*IGF2, H19*	Deregulation of imprinted genes found in 2 domains within the 11p15 region: – *IGF2* autocrine growth factor; mediator of growth hormone action, stimulator of the action of insulin (Binder et al. 2006) – *H19*: tumor suppressor (Bliek et al. 2006)	Growth, face, GU-tract, musculoskeletal, limbs, skin	Gonadoblastoma, testicular seminoma, hepatocellular carcinoma, craniopharyngioma, astrocytoma,	Concurrence
Simpson–Golabi–Behmel (Neri et al. 1998)	X-linked recessive	Xq26	*GPC3*	Cell surface heparan sulfate proteoglycan, binding to IGF2 and modulating IGF2 action (DeBaun et al. 2001)	Growth, craniofacial, brain, heart, musculoskeletal, limbs, skin	Wilms' tumor, atypical embryoma, neuroblastoma, hepatoblastoma, rhabdomyoma, hepatocellular carcinoma	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Sotos (cerebral gigantism) (Cole and Hughes 1994)	AD	5q35	NSD1	Co-regulation of transcription via interaction with steroid receptors (Wang et al. 2001b)	Growth, craniofacial, brain	Wilms' tumor, hepatocellular carcinoma, neuroblastoma, sacrococcygeal teratoma, acute lymphoblastic leukemia, lymphoma, giant cell granuloma of mandible (vaginal epidermoid carcinoma, small cell lung carcinoma)	Tumor predisposition
Trisomy 8 (Riccardi 1977)	Chromosomal	Trisomy 8	Entire chromosome 8	Unknown	Growth, craniofacial, brain, heart, GU-tract, skeleton, limbs	Wilms' tumor, leukemia	Concurrence
Trisomy 13 (Wyllie et al. 1994)	Chromosomal	Trisomy 13	Entire chromosome 13	Unknown	Growth, craniofacial, brain, neck, heart, genitalia, limbs, skin	Wilms' tumor, leukemia, neuroblastoma	Concurrence
Trisomy 18 (Baty et al. 1994)	Chromosomal	Trisomy 18	Entire chromosome 18	Unknown	Growth, craniofacial, brain, neck, heart, GU-tract, skeleton, limbs	Wilms' tumor, hepatoblastoma, neurogenic tumor	Concurrence
Tuberous sclerosis (Gomez 1991)	AD 66% de novo	9q34 16p13.3	*TSC1* *TSC2*	Inactivation of tumor suppressors tuberin and hamartin that normally inactivate the phosphatidylinositol-3 kinase (PI3K)–AKT–mTOR–S6K pathway leading to cell size increase and growth (Kwiatkowski 2003)	Brain, heart, kidney, skeleton, skin	Tubers, astrocytoma, rhabdomyoma, fibroma, angiofibroma, hemangioma of the spleen, retinal hamartoma, renal and hepatic angiomyolipomas, renal cell carcinoma, pulmonary lymphangiomyomatosis	Tumor predisposition
Turcot (Itoh et al. 1993)	AD AD AR	5q21-q22 3p21.3 7p22	*APC* *MLH1* *Biallelic mutations in PMSL2*	Tumor suppressor, mutations leading to stabilization of β-catenin in the WNT/β-catenin pathway, activating TCF transcription factors (Fearnhead et al. 2001) DNA nucleotide mismatch repair (Hemminki et al. 1994) *DNA nucleotide mismatch repair* (Nicolaides et al. 1994; Felton et al. 2007)	Brain, GI-tract	Polyposis, colon cancer, medulloblastoma, supratentorial primitive neuroectodermal tumor, glioblastoma, ependymoma, astrocytoma, oligodendroglioma, neuroblastoma, non-Hodgkin lymphoma, acute lymphoblastic leukemia	Tumor predisposition

Turner (Hall and Gilchrist 1990)	Chromosomal	X0	Entire X chromosome missing	Unknown	Growth, craniofacial, neck, chest, heart, immune system, GU-tract, skeleton, skin	Gonadoblastoma (dysgerminoma, (ganglio) neuroblastoma, schwannoma, mesenchymoma, acute myeloid leukemia, medulloblastoma, pituitary adenoma,glioma, meningioma, ,melanoma, hibernoma, thyroid carcinoma, anaplastic lung tumor, adenocarcinoma of uterus and GI tract, squamous cell carcinoma of vulva)	Tumor predisposition
Tyrosinemia type I (Kvittingen 1991)	AR	15q23-q25	*FAH*	Fumarylacetoacetate induces spindle disturbances and segregational defects (Jorquera and Tanguay 2001)	Liver, kidney, musculoskeletal	Hepatocellular carcinoma	Tumor predisposition
Unusual face, osteosarcoma, and malformation (Schuman and Burton 1979)	Uncertain	Unknown	Unknown	Unknown	Craniofacial, GU-tract	Osteosarcoma	Tumor predisposition
Von Hippel–Lindau (Lonser et al. 2003)	AD	3p25-26	*VHL*	Tumor suppressor gene; induces degradation of HIF. HIF coordinates the cell response to hypoxia by increasing expression of angiogenic, growth, and mitogenic factors including VEGF, PDGFβ, erythropoietin, and TGFα (Kaelin 2002)	Central nervous system, abdomen, GU-tract	Retinal and central nervous system hemangioblastoma, renal cell carcinoma, pancreatic tumors, pheochromocytoma	Tumor predisposition
WAGR (Wilms' tumor, aniridia, genitourinary malformations, retardation) (Riccardi et al. 1978)	Sporadic	11p13 (contiguous gene defect, including WT1 and PAX6)	*WT1* *PAX6*	Inactivation of tumor suppressor/transcription factor WT1 (Little and Wells 1997) Role in oculogenesis (Wawersik and Maas 2000)	Eyes, brain, heart, GU-tract, vertebrae	Wilms' tumor	Tumor predisposition

(continued)

Table 6.1 (continued)

Syndrome (ref)	Inheritance	Locus	Gene	(Presumed) pathogenic pathway (ref)	Body regions	Malignancies in children and adults	Nature of association
Werner (Goto et al. 1981)	AR	8p12-p11.2	*WRN*	Member of RecQ family helicases; maintenance of genome integrity (Mohaghegh and Hickson 2001)	Face, brain, endocrine system, vascular system, musculoskeletal, skin	Meningioma, paraganglioma, adenoma of the pituitary gland, thyroid and adrenal gland; basal and squamous cell carcinoma and melanoma, adenocarcinoma of thyroid, stomach, ovary, and liver, fibrosarcoma, neurofibrosarcoma, leiomyosarcoma, and osteosarcoma	Tumor predisposition
Xeroderma pigmentosum (Cohen and Levy 1989)	AR	9q22.3 2q21 3p25 19q13.2-q13.3 11p12-p11 16p13.3-p13.13 13q33	*XPA-XPG*	XP proteins are part of the nucleotide excision repair complex (Friedberg 2001)	Face, eyes, oral, brain, skin	Basal cell carcinoma, squamous cell carcinoma, melanoma, fibrosarcoma, angiosarcoma, fibroma, angioma	Tumor predisposition
47 XXY (Caldwell and Smith 1972)	Chromosomal	Extra X chromosome	–	–	Growth, craniofacial, brain, genital	Breast cancer, seminoma of testis (lymphoma, leukemia, germinoma)	Tumor predisposition

Syndromes with reported tumor incidence in childhood are listed. For each syndrome, the following items are mentioned: mode of inheritance, involved locus, responsible gene(s), (presumed) pathogenic pathway, body regions involved, and co-occurring tumors. Relatively uncommon tumors in the syndrome or in childhood are in brackets. The association of a syndrome with malignancy is given as "tumor predisposition" or "concurrence," the latter meaning that there might be an association, but data are insufficient to draw definitive conclusion

AD autosomal dominant, *AR* autosomal recessive, *GI* gastrointestinal, *GU* genitourinary

pathogenic pathway. The role of metabolic defects in cancer development and pediatric syndromes appears to be of growing importance; a few well-known examples are listed too. For details on gastrointestinal cancer predisposition syndromes refer to Chap. 30.

In recent years, it has become apparent that biallelic mutation carriers of autosomal dominant adult cancer syndromes are at a very high risk of developing specific childhood cancers often at a very young age (Rahman and Scott 2007). Biallelic mutations of BRCA2 lead to the autosomal recessive childhood cancer syndrome Fanconi anemia D1. Biallelic mutations in the mismatch repair deficiency genes MSH2, MLH1, MSH6, and PMS2 lead to a mismatch-repair-deficiency syndrome with childhood malignancies occurring at a very young age, while monoallelic mutation carriers develop hereditary nonpolyposis colorectal cancer.

6.6 Diagnostic Approach and Management in Case of Suspected Genetic Predisposition

Hereditary malignant tumors tend to occur in an earlier stage of life than the same tumor occurring sporadically. It is difficult to decide when an inherited cancer predisposition should be considered. One should suspect the presence of a tumor predisposition syndrome in case:

- An increased number of family members are diagnosed with cancer, e.g., two or more close relatives have had the same type of malignancy or two and more siblings develop a malignancy.
- A malignant tumor is diagnosed at an unusual early stage of life.
- Clustering of malignant tumors related to a known cancer syndrome is seen within a family (e.g., NCCN guidelines, link: http://www.nccn.org/index.asp).
- Clustering of rare malignant tumors (e.g., sarcomas) within a family is seen (see Table 6.1 for associated syndromes).
- More than one primary cancer is diagnosed within the patient.
- Of the presence of precursor lesions or specific benign tumors, e.g., adenomatous polyps in case of familial adenomatous polyposis, atypical, dysplastic nevi of the skin in case of hereditary melanoma, or lipomas in case of multiple endocrine neoplasia type 1.

A family tree from each side of the family should be constructed. It should include specific information on cancer types, syndromes, and other health conditions possibly related to certain malignancies. Generally speaking, the closer the relationship to the patient, the more detailed information is needed. As most familial cancer syndromes are inherited autosomal dominant, malignant tumors are found in successive generations.

In addition to the family history, the clinical examination is an essential part of a screening exam for cancer predisposition. As discussed above, half of tumor predisposition syndromes are missed by pediatric oncologists (Merks et al. 2005). Therefore, we strongly feel that all children with a malignancy should be examined by a clinical geneticist or a pediatrician skilled in clinical morphology in order to evaluate for morphological abnormalities. Internet databases and handbooks can help classifying and interpreting morphological abnormalities (Jones 2006; Winter and Baraitser 2009; Sijmons http://www.facd.info). However, those databases work best for clinical geneticists trained in this field.

After all, it is important to be aware of a possible underlying genetic predisposition in any case of rare pediatric tumor. In fact, many pediatric cancers are very rare diseases in itself, and therefore every child deserves a clinical genetic examination once in the course of its disease.

6.6.1 Management in Case of Cancer Predisposition

Familial cancer syndromes and most associated malignant tumors are extremely rare in children. Therefore, it is important to get help from physicians who are expert in the field of these rare entities, and a multidisciplinary approach has to be coordinated. Patients with genetic predisposition to cancer may have other diseases and conditions (such as endocrine disorders and immune defects) which make a comprehensive approach crucial.

Ideally, a personalized plan in order to reduce the risk of a malignancy should be developed for the patient and/or family members. This plan may include:

- Annual physical exams with additional examinations depending on the specific rare tumors that have occurred in the family
- Evaluation of any symptoms, even though they may resemble common diseases, that have persisted for

several weeks, such as abdominal pain, bone pain, growths, headaches, etc.
- Education and awareness of the signs and symptoms of cancer
- Recommendations for changes in lifestyle, such as diet, exercise, and other factors
- Genetic testing
- Participation in clinical trials to prevent and detect cancer
- Psychological support

Although genetic testing is available for many familial cancer syndromes, there are genes that have yet to be discovered. Although many hospitals in the US have a "familial cancer clinic," which is a team of health professionals with expertise in familial cancer syndromes, this is still not the case in most countries. In general, geneticists, oncologists, and social workers have to work together in order to assist individuals and families by providing risk assessment, support, screening and prevention recommendations, and genetic testing options.

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