Genetic causes of cancer predisposition in children and adolescents

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Abstract: The acquisition of *de novo* somatic mutations accounts for approximately 90% of all new cancer diagnoses, while the remaining 10% is due to inherited genetic traits. In this latter category, individuals harbouring germline mutations show a higher likelihood of developing potentially life-threatening cancers, often at a very young age. The study of cancer genetics has profoundly helped our understanding of cancer biology, leading to better characterised malignancies, tailored targeted therapies and the identification of individuals at high risk of cancer diagnosis. This review will discuss examples of cancer syndromes in children, adolescents and young adults, the main underlying gene mutations, and the use of genetic testing to identify gene mutation carriers. Finally, we will describe how gene mutation detection is employed for the life-long management of patients with high susceptibility to cancer, including genetic counselling, increased surveillance, early intervention and use of targeted therapies.

Keywords: Cancer predisposition; genetic testing; childhood cancer; adolescents

Introduction

Cancer is a multifactorial disease, with genetics being an important contributing etiologic factor. In particular, mutations influencing DNA repair genes, cell cycle regulators and cell-death pathways are the major genetic causes of malignancies (1).

The onset of cancer in an individual without an inherited cancer predisposition is due the acquisition of gene mutations in one or more somatic cells, altering the normal balance of cell proliferation, differentiation and death (2). On the other hand, an inherited cancer predisposition is a genetic condition that confers a higher likelihood of developing cancer, compared with the level of risk in the general population. In this case, the predisposing mutation(s) are passed from parents to offspring, and are therefore germline mutations (2). A particular condition that does not fall in these two categories is genetic mosaicism, where a mutation occurs in the early stages of embryonic development, leading to the presence of the mutation in only a subset of cells (3).

Inherited mutations can function in a dominant or recessive fashion, can confer different degrees of penetrance, and cause early- or late-onset disease, leading to marked variations in disease presentation within the cancer population (4). The majority of cancer predisposition genes act as tumor suppressors where mutations abrogate their function, while 10% of cancer predisposition genes (including genes encoding kinases such as ALK, KIT and MET) predispose to cancer through gain-of-function mutations (5).

The study of cancer genetics has profoundly helped in the understanding of cancer biology leading to better characterised malignancies, tailored targeted therapies, and the identification of individuals at high risk of cancer diagnosis (6). DNA-based genetic testing represents a crucial step in the identification of people with a high life-time risk of cancer, and for whom genetic counselling, screening and prevention may greatly improve either the chance of avoiding the onset of cancer, or the outcome of the disease (7). This review will provide an overview of conditions predisposing to cancer, with particular attention

to the paediatric population, relevant genetic testing used to identify such conditions, and examples of how the presence of germline cancer-predisposing mutations can alter clinical care.

Cancer predisposition in young adults

Hereditary cancer accounts for up to 10% of all cancers, with hereditary breast-ovarian cancer syndrome and hereditary non-polyposis colon cancer being the best characterised hereditary cancers. Such tumors occur in families more often than would be expected by chance, often at an uncommonly early age, and indicate the presence of a gene mutation that increases the risk of cancer (8). Many mutated genes are known to play causal roles in different cancer syndromes, and these are listed in *Table 1*.

Hereditary breast-ovarian cancer syndrome is an autosomal dominant genetic condition caused by germline mutations in the *BRCA1* and *BRCA2* tumor suppressor genes (8,14). This disorder confers a higher risk of breast and ovarian cancer in women, and prostate cancer in men (14). In an analysis of over 8,000 index cases, the average cumulative risk in *BRCA1*-mutation carriers was 65% for developing breast cancer, and 39% for developing ovarian cancer by 70 years of age (15). The corresponding estimates for *BRCA2* were 45% and 11%, respectively (15), although the penetrance of individual *BRCA1* and *BRCA2* gene mutations varies considerably (14). The relative risk of developing breast cancer is highest for *BRCA1* mutation carriers between 30-39 years of age, whereas ovarian cancers tend to be diagnosed later (15). In contrast, relative risk estimates for breast cancer do not vary according to age for *BRCA2* mutation carriers (15). For those individuals who are mutation carriers, several screening and primary prevention options have been suggested, including prophylactic surgery and chemoprevention (14). In the last few years, DNA sequencing has identified other rare loss-of-function variants that confer moderate risks of breast and/or ovarian cancer, in genes including *PALB2* (16), *ATM* (17), *BRIP1* (18), *CHEK2* (19) and *RAD51C* (20), and the p53 inducible protein phosphatase *PPM1D* in a mosaic form (21).

Hereditary non-polyposis colon cancer, also known as Lynch syndrome, is another autosomal dominant cancer syndrome caused by genetic mutations in DNA mismatch repair genes (such as *MLH1*, *MSH2*, *MSH6* and *PMS2*), that increase the risk of early development of a number of tumors including colorectal, stomach and pancreatic cancer (22). Defective mismatch repair leads to microsatellite instability and frame-shift mutations in genes involved in tumor initiation and progression (22). Lynch syndrome accounts for some 2-4% of colorectal cancers, and the reported lifetime risk of colorectal cancer varies between 38-100% for men with DNA mismatch repair mutations, and between 24-54% for women (23). Age-specific cumulative risks for colorectal cancer also vary considerably according to patient gender, and the specific mismatch repair gene that is mutated (23).

Cancer predisposition in children and adolescents

Compared with those tumor suppressor and DNA repair genes mutated in hereditary breast-ovarian cancer and hereditary non-polyposis colon cancer syndrome, mutations in other cancer predisposition genes can lead to cancer diagnoses at even younger ages. According to a recent publication by Rahman, a total of 114 cancer predisposition genes have been discovered in the past 30 years (24). Interestingly, 16 of these can cause both autosomal dominant and recessive conditions, with the recessive pattern of inheritance of a subset of these genes being associated with high risk of developing childhood cancer (24). Eight examples of cancer syndromes causing paediatric tumors will be described in the following sections. The first two (Fanconi anemia and Xeroderma pigmentosum) have a recessive pattern of inheritance, followed by four examples of dominant inheritance patterns (retinoblastoma, Li-Fraumeni syndrome, DICER1 syndrome and neurofibromatosis), one RAS mosaic condition, and Down syndrome.

Fanconi anemia

Fanconi anemia is characterised by congenital abnormalities, bone marrow failure, and a higher risk of developing myeloid and solid malignancies, such as squamous cell carcinoma and liver tumours, including adenoma and hepatocellular carcinoma (25,26). The median age for cancer diagnosis in Fanconi anemia patients has been reported as 16 years (25), and the cumulative probability of a solid tumor diagnosis is 75% by the age of 45 years (25). Indeed, there is a 500-fold increase in the incidence of head and neck squamous cell carcinoma in Fancomi anemia patients (27). The Fanconi anemia pathway counts 16 potentially mutated genes (including *BRCA2*, previously

Table 1 Known cancer syndromes with patterns of inheritance, involved gene/s, and histological tumor types or main development sites (9-13)

	Cancer syndrome	Mutated gene/s	Main tumor type/site
X-linked recessive	Simpson Golabi Behmel syndrome	GPC3	Wilms' tumor, hepatoblastoma
	X-linked lymphoproliferative disease	SH2D1A	Lymphomas
Autosomal recessive	Ataxia telangiectasia	ATM	Lymphomas, leukemia
	Bloom syndrome	BLM	Multiple types
	Fanconi anemia	FANC family	AML
	MUTYH-associated polyposis	MUTYH	Colon
	Nijmegen breakage syndrome	NBN	Lymphomas
	Rothmund-Thomson syndrome	RECQL4	Osteosarcoma
	Werner syndrome	WRN	Melanoma, sarcoma
	Xeroderma pigmentosum	XP family	Skin
Autosomal dominant	Adenomatous polyposis, familial	APC	Colon
	Beckwith-Wiedemann syndrome	IGF-2 or CDKN1C	Multiple types
	Birt-Hogg-Dubé syndrome	FLCN	Renal
	Canale-Smith syndrome	FAS	Lymphomas
	Cardio-facio-cutaneous syndrome	BRAF/KRAS	ALL
	Carney syndrome	PRKAR1A	Testicular
	CBL syndrome	CBL	JMML
	Costello syndrome	HRAS	Rhabdomyosarcoma
	Cowden syndrome	PTEN	Multiple types
	Dicer1 syndrome	DICER1	Pleuropulmonary blastoma
	Dysplastic nevus syndrome with familial melanoma	CDKN2A	Melanoma
	GATA2 haploinsufficiency syndrome	GATA2	AML
	Gorlin syndrome	PTCH1/SUFU	Basal cell carcinoma/ medulloblastoma
	Hereditary breast-ovarian cancer syndrome	BRCA1/2	Breast/ovary
	Hereditary diffuse gastric cancer	CDH1	Gastric
	Hereditary leiomyomatosis renal cell cancer	FH	Renal
	Hereditary papillary renal cell cancer	MET	Renal
	Hereditary paraganglioma-pheochromocytoma syndrome	SDH family	Paraganglioma-pheochromocytoma
	Howel-Evans syndrome	RHBDF2	Eosophageal
	Juvenile polyposis syndrome	BMPR1A and SMAD4	Colon adenocarcinoma
	Leopard syndrome	PTPN11/RAF1	AML
	Li-Fraumeni syndrome	TP53	Multiple types
	Lynch syndrome	MLH1, MSH2, MSH6, PMS2	Colorectal, multiple types
	Multiple endocrine neoplasia type 1/2	MEN1, RET	Endocrine glands
	Multiple osteochondromatosis	EXT family	Bones
	Neurofibromatosis type 1/2	NF1/2	Brain/spine
	Noonan syndrome	PTPN11/SOS1/RAF1	Neuroblastoma/JMML/ALL
	Peutz-Jeghers syndrome	STK11/LKB1	Colon/bowel, multiple types
	Prostate cancer, familial	HPC1, BRCA1/2	Prostate
	Rhabdoid Tumor Predisposition	SMARCB1, INI1	Rhabdoid tumor
	Retinoblastoma	RB1	Retinoblastoma
	Sotos syndrome	NSD1	Neuroblastoma
	Severe congenital neutropenia	RUNX1	AML
	Tuberous sclerosis	TSC1/2	Astrocytoma
	Von Hippel-Lindau disease	VHL	Renal, multiple types
	Wilms' tumor syndromes	WT1	Nephroblastoma

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; JMML, juvenile myelomonocytic leukemia; ATRT, atypical teratoid/ rhabdoid tumor.

known as *FANCD1*) (28). Subsets of Fanconi anemia proteins are known to form complexes allowing protein ubiquitination, and subsequent DNA repair activation (28). Thus, while Fanconi anemia has been historically considered a disease of inter-strand cross-link sensitivity, Fanconi anemia proteins are now known to intersect with several distinct DNA repair pathways (28).

Xeroderma pigmentosum

A second example of an autosomal recessive disorder causing increased risk of skin cancers is Xeroderma pigmentosum, a rare condition characterized by increased sensitivity to UV light, and neurodegeneration. Xeroderma pigmentosum is the result of mutations in the *XP* nucleotide excision repair family of genes (29), and affected individuals have a more than 10,000-fold elevated risk of non-melanoma skin cancer, including melanoma (30).

Retinoblastoma

Retinoblastoma is a malignant tumor of the embryonic neural retina and the most common paediatric cancer of the eye. It usually affects young children, with more than 90% of cases diagnosed before 5 years of age (31). Mutations in the well described *RB1* tumor suppressor are the genetic cause of retinoblastoma, and two main clinical forms have being described. Unilateral retinoblastoma accounts for approximately 75% cases and is due to sporadic *RB1* mutations (31). The remaining 25% patients with bilateral disease carry a germline *RB1* mutation (31), and are at high risk of developing second malignancies, especially sarcomas and melanoma. These individuals will require cancer surveillance throughout their life, and treatments will need to be tailored to avoid radiotherapy. In patients with bilateral retinoblastoma, only 25% inherit an *RB1* mutation from an affected parent, whereas the remaining 75% of cases result from *de novo RB1* mutations (31). In a small proportion of patients with germline *RB1* mutations, retinoblastoma is also associated with pineoblastoma and other malignant midline supratentorial primitive neuroectodermal tumors (32). These cases have been described as trilateral retinoblastoma, and have historically shown very poor outcomes (32).

Li-Fraumeni syndrome

Li-Fraumeni syndrome is an autosomal dominant cancer syndrome caused by heterozygous germline mutations in the *TP53* gene. It is characterised by the development of rare tumors in childhood and multiple common cancers of unexpectedly early onset in adulthood. In particular, 50% of patients with Li-Fraumeni syndrome develop at least one malignancy by 30 years of age, and one third of cancer survivors will develop multiple primary cancers over their lifetime (33).

TP53 is the most frequently mutated gene in human cancer and acquired *TP53* mutations are also associated with diminished survival rates, increased resistance to chemotherapy and radiation, and elevated relapse rates (34). *TP53* encodes a transcription factor with regulatory functions that promote DNA repair and tumor suppression. Most *TP53* mutations are missense alterations clustered at codons 175, 248 and 273 in the central DNA-binding domain (35), and are considered to be highly penetrant. For example, *TP53* mutations in the DNA-binding domain lead to a cancer diagnosis in 73% of men and nearly 100% of women during their lifetime (36), with cumulative 21% and 49% risks, respectively, of developing cancer before the age of 30 years (37). However, the R337H *TP53* mutation only conferred an 11% risk of childhood adrenocortical cancer, as opposed to other classic Li-Fraumeni syndrome malignancies (38). Two other aspects of TP53 function may be relevant in children, namely telomere shortening and chromothripsis. Shorter telomeres were noted in *TP53* mutation carriers that developed cancer either during childhood or adulthood, compared with non-affected controls (39). In addition, genome sequencing of medulloblastoma demonstrated associations between large catastrophic chromosome rearrangements, or chromothripsis, and mutations in *TP53* (40).

DICER1 syndrome

Pleuropulmonary blastoma is a rare paediatric lung cancer of embryonal origin, and has been associated with germline *DICER1* mutations (41). *DICER1* encodes the endoribonuclease Dicer, a helicase enzyme which cleaves double-stranded RNA and pre-microRNA into small interfering RNA and microRNA, respectively, facilitating the activation of the RNA-induced silencing complex (42). *DICER1* is therefore crucial for embryogenesis and early development (42,43). Forty different heterozygous germline *DICER1* mutations have been reported in pleuropulmonary blastoma and other rare tumors of childhood, including cystic nephroma, ovarian Sertoli-Leydig cell tumor,

embryonal rhabdomyosarcoma, supratentorial primitive neuroectodermal tumor and multinodular goiter (43).

Neurofibromatosis type I

Disorders described as neurofibromatoses represent three genetically distinct conditions which share an increased likelihood of cancer development, especially peripheral nerve sheath tumors and gliomas (44). Neurofibromatosis type I, the most common form of neurofibromatosis, is characterised by the development of benign neurofibromas on or around peripheral nerves (44), whereas in neurofibromatosis type II, the vestibulocochlear nerve develops schwannomas. In the third condition, Schwannomatosis, schwannomas develop on cranial, spinal and peripheral nerves (44).

Neurofibromatosis type I is associated with mutations in the *NF1* gene that function in an autosomal dominant fashion (45). NF1 is responsible for the regulation of cell division through the inactivation of RAS-GTP, a fundamental step in the regulation of the RAS and PI3K pathways. In the absence of NF1, signaling is increased through these pathways, resulting in cell proliferation and inhibited apoptosis (45). Approximately half of all neurofibromatosis type I cases are diagnosed without a known family history, and are thought to represent sporadic *NF1* mutations (46).

RASopathies and mosaic RAS mutations

A number of other developmental syndromes are associated with RAS pathway deregulation and are collectively referred to RASopathies (47). Somatic mutations in *RAS* subtypes occur frequently in human cancers, and germline mutations in these genes are the cause of complex syndromes with increased susceptibility to cancer, such as Noonan syndrome, Costello syndrome, Leopard syndrome and cardio-facio-cutaneous syndrome (48). The genetic characteristics of these conditions and their relationships with cancer development are listed in *Table 1*. While having some different features, RASopathies have common characteristics including dysmorphic appearance, skin abnormalities, congenital heart disease and an increased risk of malignancies (47). For example, embryonic rhabdomyosarcoma and neuroblastoma develop in up to 20% of Costello syndrome patients (49).

RAS mosaicism occurs when mutations are acquired during the post-zygotic stage, leading to the presence of the mutation in only a subset of cells (50). Often, this condition

is identifiable because of the presence of birthmarks such as epidermal nevi or hemangiomas (51), and may confer a predisposition to cancer, according to Knudson's "two hit" theory (50). Although malignant tumors have only rarely been reported in association with epidermal nevi, the risk of cancer might depend on the extent of mosaicism, the tissues involved, and the specific gene mutation. Also, children who are mosaic for *RAS* mutations but do not present with skin birthmarks may never be identified as such (50,52). Oncogene mutation mosaicism may therefore contribute to cancer causation to a greater extent than is presently appreciated.

Down syndrome

Down syndrome, or constitutional trisomy 21, is the most common human aneuploidy syndrome, and affected children have an elevated risk of acute leukemia which is up to 500-fold higher than that of the general population (53). Approximately 1% of children with Down syndrome develop spontaneously regressing transient myeloproliferative syndrome, acute myeloid leukaemia of Down syndrome, and/or B-lineage acute lymphoblastic leukaemia (53,54), which are commonly linked to dosage effects of chromosome 21 genes (54). Interestingly, acquired trisomy or tetrasomy 21 with the involvement of *RUNX1* at chromosome 21q22 has also been described in many children with sporadic leukemias (55).

Trisomy 21 likely contributes to the development of *GATA1* mutations, which are a feature of transient myeloproliferative syndrome, and also contribute to acute myeloid leukemia (AML) of Down syndrome (54). *GATA1* mutations may also be responsible for the sensitivity of this disease to therapy, which is characterised by high cure rates (54). The molecular etiology of B-precursor acute lymphoblastic leukaemia in Down syndrome is very different, as *GATA1* mutations are not detected, and clinical outcomes are worse than in patients without Down syndrome (54). B-precursor acute lymphoblastic leukaemia in Down syndrome is characterised by *IKZF1* deletions and *JAK2* tyrosine kinase mutations, the latter highlighting the possibility of targeted therapy for these patients (56).

Genetic testing and patient management

The guidelines for referring cancer patients to genetic testing have changed over the years. For example, since their description, the definitions of Li-Fraumeni and Li-

fraumeni-like syndromes have been refined, notably by Chompret *et al.* (57), where *TP53* mutations were expected to be identified in 20% of cases. In a subsequent study, 29% of patients meeting Chompret's criteria (57) were identified as *TP53* mutation carriers (58). DNA sequencing methods also have evolved from gene-specific tests using Sanger sequencing to whole exome or genome next-generation sequencing (59). With the use of next-generation sequencing, the number of recognised cancer predisposing mutations has dramatically increased, and has allowed genetic information to be associated with other medical conditions or drug responses (60).

Genetic testing of cancer patients and their relatives has helped to identify at-risk family members, thereby introducing surveillance and early intervention, and improving survival rates for familial cancers. As an example, a prospective study of asymptomatic germline *TP53* mutation carriers showed 100% overall patient survival at 3 years in the enhanced surveillance group, compared with only 21% overall survival in the routine follow-up group (61). Given the complexity and gravity of Li-Fraumeni syndrome, guidelines and recommendations for patient management are extensive, and in addition to an annual physical examination, include age-specific breast cancer monitoring (or preventive mastectomy), colonoscopy every 2-5 years beginning no later than 25 years of age, and organ-targeted surveillance, based on cancers diagnosed in the family (62).

Point mutations in codon 918 of the *RET* oncogene have been identified in 98% of patients with multiple endocrine neoplasia type 2 (MEN2) (63). Thyroidectomy is recommended within the first 6 months of life, since codon 918 mutations are associated with early onset medullary thyroid cancers (63). For children with neurofibromatosis type I, annual surveillance for ocular signs of optic nerve glioma is recommended until 10 years of age, while annual blood pressure measurement is recommended for phaeochromocytoma detection (64). Individuals with neurofibromatosis type II are frequently screened to detect early acoustic neuroma, since surgery for hearing preservation has best chance of success when lesions are small at diagnosis (65). Similarly, the detection of *RB1* mutations and early treatment of retinoblastoma has been shown to increase ocular retention and preserve vision (66), while screening for pineal tumors has increased the 5-year survival of trilateral retinoblastoma from 0% to 27% (67). Since the risk of developing Wilms' tumor can be as high as 50% in children harbouring germline *WT1* alterations, frequent renal ultrasounds are recommended from the age

of syndrome diagnosis up to 5-7 years of age (68). Another example of successful intervention is the improved quality of life in children with familial adenomatous polyposis through enrolment on chemoprevention trials with celecoxib, which led to reduced colorectal polyp formation and delayed colectomies (69). Moreover, offering these patients prophylactic surgery significantly reduces mortality from colorectal cancer (70).

The growing use of genome-wide screening (71) and next-generation sequencing methods brings with it the possibility of identifying unexpected cancer-predisposing gene mutations, for example in members of unaffected families who have acquired *de novo* variations, as well as variations of unknown significance (72). These increasingly frequent scenarios highlight the importance of ethical approaches to the disclosure of incidental findings (73), and the psychological support needed by patients and families affected by cancer syndromes (74).

Conclusions

Although tumor predisposition underlies a comparatively small proportion of childhood cancer cases, the early age of diagnosis suggests that inherited cancer predisposition may underly a greater proportion of cases than is currently appreciated (69). The continued application of next-generation sequencing to childhood cancer patients and their family members will be expected to identify mutations in known cancer predisposition genes that have been previously associated with early onset adult cancer, as well as germline mutations in genes that are known to be somatically mutated in the same or other cancer types. Previously unrecognised tumor predisposition genes may also be uncovered through the study of patients with very rare cancers and/or unusual clinical presentation or features. Our current understanding of the genetic basis of tumor predisposition has already allowed the development of genetic tests that can assist in planning a life-long series of interventions that can include counselling, prevention, surveillance and early treatment, in the event of a cancer diagnosis. Expanding our knowledge of the genetic basis of cancer predisposition in children will have the exciting consequence of extending these benefits to larger numbers of patients and their families.

Acknowledgements

the Kids Cancer Alliance from the Cancer Institute NSW (Grant ID: 11/TRC/1-03), and from the University of Sydney.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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