Received: 28 February 2020 | Revised: 30 March 2020 | Accepted: 31 March 2020

DOI: 10.1002/pbc.28335

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

REVIEW

Why do young people get cancer?

Alex Kentsis

Sloan Kettering Institute and Department of Pediatrics, Weill Medical College of Cornell University and Memorial Sloan Kettering Cancer Center, New York, New York

Correspondence
Alex Kentsis, Sloan Kettering Institute and Department of Pediatrics, Weill Medical College of Cornell University, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065.
Email: kentsisresearchgroup@gmail.com

Funding information
National Cancer Institute, Grant/Award Number: R01 CA214812

Abstract

Oncologists and cancer biologists are frequently confronted by the question of what causes cancer? This is particularly vexing for cancers affecting children and young adults who have had limited exposure to environmental mutagens and the effects of aging. Here, I focus on a general framework of the causes of early-onset cancer development in children and young adults by relating inherited and constitutional cancer predisposition, oncogenic pathogens, and developmental mutations. This framework has implications not only for mechanistic investigation of young cancers, but should also clarify improved strategies for their treatment, screening, and potential prevention.

KEYWORDS
oncogenes, oncology, pediatric hematology/oncology, tumor biology

1 | INTRODUCTION

The causes of human cancer have fascinated physicians and biologists alike. Foundational cell biological studies have implicated both intrinsic sources of mutations in the form of genomic instability, as well as exogenous mutators such as oncogenic viruses. These studies provided important concepts for explaining cancer pathogenesis in select cases. Likewise, human epidemiological studies led to the multistage model of cancer pathogenesis based on the patterns of age-dependent incidence of cancers in various human tissues. More recently, these models incorporated quantitative estimates of mutational rates in various cell types, as well as inheritance of cancer-predisposing alleles that increase the risk of accumulating oncogenic mutations.

The current multistage model explains the age-increasing incidence of cancer due to the somatic acquisition of mutations involving oncogenes and tumor suppressor genes, which in specific combinations leads to malignant transformation in susceptible cell types. Consistent with this model, exposure to mutagens or inheritance of alleles that affect cellular DNA damage repair, genomic integrity, and cell growth and proliferation can accelerate cancer development, causing cancers in younger individuals. Among cancers that tend to affect aging adults, the majority of cancer risk is due to the apparently stochastic acquisition of mutations in replicating tissues. In contrast, the causes of cancer in children and young adults are a product of the interaction among inherited or constitutional cancer predisposition, endogenous developmental mutational processes, and exposure to factors that regulate them, including environmental mutagens and oncogenic pathogens. Here, I summarize the current evidence for these processes in human cancer and develop a general framework of the causes of early-onset cancer development in children and young adults by relating inherited or constitutional cancer predisposition, oncogenic pathogens, and developmental mutations.

Abbreviations: ALL, acute lymphoblastic leukemia; CMMRD, constitutional mismatch-repair deficiency; EBV, Epstein-Barr virus; HPV, human papilloma virus; HTLV, human T-cell lymphotropic virus.

2 | CONSTITUTIONAL CANCER PREDISPOSITION

The original studies of the development of retinoblastoma—a tumor that mostly affects infants—have revealed the essential functions that inherited mutations play in the predisposition of some individuals to cancer at a relatively young age.[1] We now recognize that many tumor suppressor and oncogenes that are somatically mutated in human cancers are mutated constitutionally, as a result of either familial inheritance or de novo germline or mosaic mutations, conferring increased susceptibility to cancer at a young age.[2-4] Such cancer predisposition genes can be classified into distinct pathologic classes, based on the molecular consequences of their mutations, leading to the dysregulation of (i) mitotic cell division, (ii) DNA damage repair, and (iii) developmental signaling and gene expression (Figure 1).

For example, RB1, APC, and TP53 in part control cell-cycle progression, and cells with inactivating mutations of these genes undergo

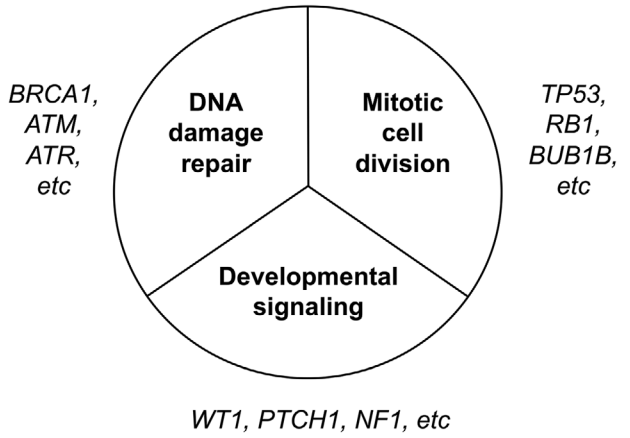

FIGURE 1 Mechanisms of inherited cancer predisposition

defective mitosis with genomic instability. This generates or propagates aneuploid tumor-initiating cells with chromosomal rearrangements that cause mutations of additional genes required for tumor development. Resultant tumors, including retinoblastomas, osteosarcomas (*RB1*), medulloblastomas, colon carcinomas, hepatoblastomas (*APC*), and a variety of brain tumors, sarcomas and leukemias (*TP53*), exhibit extensive chromosomal abnormalities that have stereotypic features that have now been documented in recent genomic studies of these malignancies.[5]

Similarly, genes that encode factors that function in the repair of DNA damage that can occur during normal cell growth and development are also mutated constitutionally in predisposed children and adults, leading to the accumulation of mutations that ultimately involve tumor suppressor and oncogenes causing early-onset tumor development. This includes DNA mismatch-repair factors MLH1, MSH2, MSH6, and PMS2, base excision repair factor MUTYH, homologous recombination repair factors BRCA1, BRCA2, RAD51C, RAD51D, and PALB2, double-strand break repair factors ATM and ATR, and several others, as reviewed recently.[6,7] Many of these germline gene mutations contribute to recognized familial cancer predisposition syndromes, including hereditary breast-ovarian-prostate cancer, Bloom syndrome, Fanconi anemia, ataxia-telangiectasia, Nijmegen breakage syndrome, Werner syndrome, Lynch syndrome, Rothmund-Thomson syndrome, and xeroderma pigmentosum, among others. Individuals with inherited biallelic and monoallelic mutations of these genes develop various types of carcinomas, sarcomas, leukemias, and lymphomas, both in childhood and adulthood. For example, inheritance of biallelic mutations of the mismatch-repair genes such as MLH1 causes multiple tumors in infancy and young childhood as part of the constitutional mismatch-repair-deficiency (CMMRD) syndrome. In contrast, their inherited monoallelic mutations cause Lynch syndrome, predisposing to cancer development in adulthood. Importantly, the specific features and genome-wide signatures of the DNA mutations that result from distinct DNA damage repair defects can be used to develop genotype-phenotype associations. This can be used not only to define the penetrance of different mutant alleles but also to diagnose these conditions clinically. For example, individuals without obvious family history of cancer predisposition could be identified in prospective or molecular studies based on the detection of new germline alleles.[5]

Finally, various genes that encode factors that regulate signaling and gene-expression controlling cell development and differentiation can also be mutated constitutionally, causing early-onset developmental cancers. For example, RET, ALK, NF1, NF2, TSC1, TSC2, PTEN, STK11/LKB1, and PTCH1 regulate developmental cell-surface receptor signaling and exhibit germline mutations in children and adults predisposed to the development of carcinomas, gliomas, leukemias, and medulloblastomas. Similarly, constitutional mutations of *WT1*, *DICER1*, *SMAD4*, *SMARCB1*, and *VHL* cause dysregulated gene expression either transcriptionally or posttranscriptionally, predisposing individuals to Wilms and other kidney tumors, carcinomas, soft-tissue sarcomas, and hemangioblastomas. Depending on the specific properties of particular mutations, the cells in which tumorigenesis is initiated, and possible environmental exposures, these inherited or constitutional mutations can present with clinically diagnosed malignancies in either childhood or young adulthood.

Although the original studies of familial cancer predisposition have identified such mutations in individuals with known family history, germline mutations in individuals with no obvious family histories have also been identified, as accelerated by recent advances in genome sequencing. Currently, it is estimated that as many as 10% of children and adults with apparently sporadic cancers involve an underlying inherited or constitutional predisposing genetic mutation.[8-11] Ongoing studies should reveal the spectrum of familial cancer predisposition mutations and alleles, as well as de novo germline or mosaic mutations that predispose to cancer development.[12,13] Increasingly, testing and screening for specific inherited predisposing mutations are recommended for at risk populations. This is justified given the substantial prevalence of constitutional genetic mutations in specific populations and tumor types, such as constitutional *TP53* mutations in children with anaplastic rhabdomyosarcomas, medulloblastomas, diffusely anaplastic Wilms tumors, adrenocortical and choroid plexus carcinomas, mutations of *BRCA2* in young adults with breast, ovarian, or prostate carcinomas, and CMMRD mutations in infants with glioblastomas. This has immediately actionable implications for individual therapy, such as avoidance or minimization of radiotherapy (*TP53* mutations), the use of PARP inhibitors (*BRCA2* mutations) and immune-checkpoint inhibitors (CMMRD). Similarly, various surveillance and counseling protocols are currently being used or investigated for the early detection and prevention of cancers in predisposed individuals and families.[11,14]

3 | ENVIRONMENTAL MUTAGENS

Even for individuals with inherited or constitutional cancer predisposition, the risk of cancer development is strongly dependent on environmental exposures, such as exposure to sunlight in individuals with xeroderma pigmentosum that causes skin carcinomas due to UV-induced DNA thymine dimer mutations with impaired nucleotide excision repair (Figure 2). Similarly, exposure to environmental mutagens

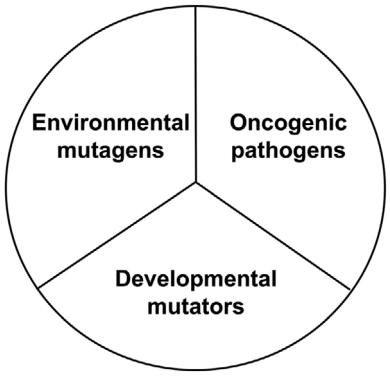

FIGURE 2 Causes of oncogenic mutations in early-onset cancers

has been linked to early-onset cancer development. This includes lung carcinomas due to air-borne radon or tobacco smoke exposures, and mesotheliomas due to air-borne asbestos exposure (as also modulated by inheritance of germline *BAP1* mutations). In addition, urothelial, liver, and stomach carcinomas can be caused by the food-borne exposures to the DNA alkylator aristolochic acid, enzymatic inhibitor of the tumor suppressor protein phosphatase 2A okadaic acid, and DNA alkylator aflatoxins, respectively. Similarly, topoisomerase inhibitors such as etoposide that are used as chemotherapeutic drugs can promote cancer development by induction of chromosomal translocations that lead to the production of oncogenic fusion proteins in cases of therapy-related acute myeloid leukemias. Various naturally occurring compounds have also been implicated as potential topoisomerase inhibitors, though the epidemiological and biochemical evidence for this phenomenon is varied. Because environmental mutagens appear to function either by direct induction of DNA damage or by inhibiting factors that repair endogenous DNA damage, it is also possible that environmental exposures could contribute to cancer pathogenesis in children and young adults by affecting intrinsic mutational processes in our cells.

4 | ONCOGENIC PATHOGENS

Epidemiologic studies have also documented diverse pathogens that contribute to the induction or promotion of various malignancies. For example, infections by the human papilloma viruses (HPV) cause carcinomas of the cervix and oropharynx in young adults as a result of the expression of viral proteins that can directly inhibit the function of TP53 and other cellular tumor suppressor proteins. Similarly, Epstein-Barr virus (EBV) infections cause lymphomas and nasopharyngeal carcinomas; Merkel cell polyomavirus causes Merkel cell carcinomas; and human T-cell lymphotropic virus (HTLV) can cause leukemias. Epidemiologic studies have reported various geographic and temporal clustering of childhood leukemias, raising the possibility that infectious causes contribute to childhood cancer risk, based on the existence of avian, rodent, and mammalian leukemia viruses. Studies to date have failed to identify specific pathogens responsible for these epidemiologic phenomena. However, infectious exposures are linked to the pathogenesis of childhood leukemias, insofar as the activity of developmental mutators RAG1/2 and AID is regulated by immune signaling. Nonetheless, it is likely that additional human oncogenic pathogens will be discovered as a result of genomic studies, as bolstered by the use of improved methods for genome sequencing and assembly. For example, recently *Fusobacterium* growth has been associated with the development of colorectal carcinomas.[15] Similarly, increased incidence of distinct cancers in distinct geographic regions and patient populations is likely to yield new and unanticipated environmental mutagens. This should have immediate implications for the prevention and treatment of these malignancies, as well as discovery of fundamental mechanisms of cancer pathogenesis.

5 | DEVELOPMENTAL TUMORIGENESIS AND ENDOGENOUS MUTATORS

What is responsible for the incidence of cancer in the majority of children and young adults? Although additional genomic and epidemiologic studies will surely lead to the identification of new constitutional genetic mutations and environmental mutagens and pathogens, analysis of human cancer incidence suggests that these causes explain only a subset of early-onset cancers. Original studies of the age distribution of human cancer noted a strong correlation between cancer incidence and the power of its age of incidence, explained by the multistage model of somatic mutation selection.[16] Recent refinements of this model involve the expansion of stem or progenitor cells that accrue mutations, followed by their somatic selection and accumulation to ultimately induce cancer.[17] This model accurately explains the age-dependent increase in the incidence of distinct cancers, such as colorectal carcinomas, that steadily increase in incidence with a peak in older adulthood. Although many human cancers exhibit similar age-dependent incidence profiles, other cancers tend to occur preferentially in infants, children, adolescents, or young adults, such as lymphoblastic leukemias, Hodgkin lymphomas, astrocytomas, ependymomas, medulloblastomas, osteosarcomas, Ewing sarcomas, Wilms tumors, rhabdomyosarcomas, germ cell tumors, and neuroblastomas, based on the analysis of recent SEER incidence data (12 of 38 tumor types; Supporting Information Table S1).

In addition to the potential inheritance of cancer-predisposing mutations and exposure to environmental mutagens or oncogenic pathogens, the peaking incidence of specific cancers in childhood or young adulthood can be explained by two non-mutually exclusive mechanisms: (i) presence of a stem or progenitor cell population that has impaired DNA damage repair capacity during proliferative DNA replication and/or (ii) activation of endogenous DNA nucleases or other biochemical processes that induce mutations during specific developmental periods.[18] Although DNA damage and its repair are intrinsically linked, these two mechanisms would be expected to produce different types of mutations and genome-wide signatures in resultant tumors.

Indeed, recent studies of acute lymphoblastic leukemias (ALL) that predominantly affect young children have identified specific

sequences near the breakpoint junctions of chromosomal translocations that mutate leukemia oncogenes, such as the ETV6-RUNX1 fusion.[19] Numerous chromosomal rearrangements that occur somatically in ALL cells involve specific DNA sequences that are the substrates for the RAG1/2 DNA recombinase.[20] Supporting the causal function of the RAG1/2-induced mutations in ALL induction, deficiency of RAG1/2 prevents leukemia development in mouse models.[21] Normally, RAG1/2 activity is controlled during B- and T-cell development to mediate somatic DNA rearrangements, leading to the immune diversification of antibodies and T-cell receptors. At least in part, this regulation is linked to inflammatory signaling, which is consistent with the epidemiologic link between infectious exposures and the development of ALL in childhood.[22] Indeed, infection exposure and inflammatory signaling are causal factors in mouse models of acute lymphoblastic leukemias.[21,23] Recently, somatic deamination of cytosine to uracil has been observed in various human cancers, including B-cell lymphomas.[24] This process is catalyzed by the APOBEC-family deaminases, and AID in particular, which is activated in developing B cells. Indeed, ectopic activation of AID is sufficient to induce mutagenic uracil mismatches, similar to the mutational signatures observed in distinct human lymphomas. In fact, kataegis-associated clustered lymphoid cancer mutation hotspots contain predominantly AID mutational signatures.[25] In all, dysregulation of RAG1/2 and AID enzymes is responsible for the induction of somatic mutations that mediate the development of lymphoid lymphomas and leukemias, thereby explaining their early onset in children and young adults, even in the absence of inherited or constitutional cancer predisposition or mutagen exposure.

Although the activities of RAG1/2 and AID help to explain the early-onset of lymphoid malignancies, they are generally not expressed in the majority of other cancers with young incidence peaks. Remarkably, the majority of medulloblastomas, neuroblastomas, ependymomas, Ewing and various other sarcomas such as rhabdoid tumors instead express PGBD5 that is enzymatically similar to the RAG1/2 DNA recombinase.[26,27] Both PGBD5 and RAG1/2 are domesticated DNA transposases that use a triad of aspartic acids to mediate sequence-specific double-strand DNA beaks and rearrangements.[28] The activity of PGBD5 has been studied in human rhabdoid tumors, where it appears to mediate sequence-specific deletions and additional mutations of tumor suppressor genes, including *SMARCB1* itself, which is the defining feature of rhabdoid tumor pathogenesis.[29] Importantly, the mutagenic activity of PGBD5 confers susceptibility to targeted inhibitors of DNA damage repair signaling in rhabdoid tumor, medulloblastoma, neuroblastoma, and Ewing sarcoma cells, providing new potential therapeutic strategies for patients.[30] The presence of active mutagenic PGBD5 DNA transposase in the majority of childhood and young adult solid tumors is expected to contribute to the induction of somatic DNA rearrangements, some of which can be oncogenic. Recent studies have implicated the developmental origins of childhood cancers, and identified distinct mutational patterns and genomic features that distinguish them from adult-onset cancers associated with aging.[31,32] Analysis of mutational signatures of childhood and young adult tumors, as compared with the somatic mutations and mosaic DNA rearrangements that accompany normal tissue development, should lead to the identification of developmental mutators that contribute to early-onset incidence of cancers in children and young adults.[18,26]

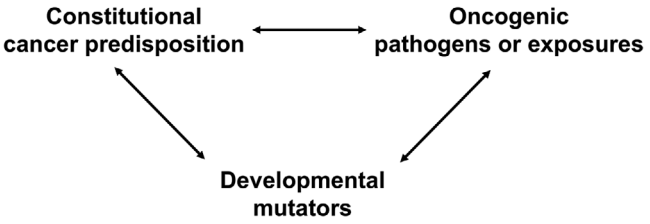

FIGURE 3 Possible interactions among inherited or constitutional cancer predisposition, oncogenic pathogens, and developmental mutations

6 | CONCLUSIONS AND FUTURE DIRECTIONS

The developmental mutator model would predict that additional endogenous mutators, inherited or constitutional alleles influencing cellular mutational rates, or environmental exposures and oncogenic pathogens should be found in human cancers with young incidence peaks, not explained by PGBD5, RAG1/2, and AID or known cancer predisposition alleles. This includes astrocytomas and other glial tumors that affect children and young adults, osteosarcomas, germ cell tumors, infant fibrosarcomas, retinoblastomas, and Wilms tumors among many others. It is expected that the patterns of somatic mutations observed in these tumors would be specifically related to the underlying developmental mutational process, e.g., impaired repair of DNA damage induced by sustained DNA replication and cell proliferation versus distinct mutational signatures of endogenous mutators such as developmentally induced DNA nucleases.

Indeed, human cancers exhibit more than 50 mutational patterns involving nucleotide substitutions and more than a dozen classes of DNA rearrangements.[33,34] At least some of the underlying causes may be revealed by the classification of specific mutational signatures in the genomes of early-onset cancers. Stratification of patients by these mutational processes can be incorporated into clinical trials of emerging targeted inhibitors of DNA damage repair signaling and immunotherapies. Similarly, fundamental mechanisms of cancer pathogenesis may be revealed by the focused study of cancers with similar incidence peaks but divergent causes, such as oropharyngeal carcinomas that occur in young patients without evidence of HPV infection or tobacco smoke exposure.

Although the three mechanisms of early-onset cancer development were outlined separately, they are expected to interact (Figure 3). For example, approximately one third of infants with rhabdoid tumors that exhibit evidence of PGBD5 DNA transposase–induced developmental somatic mutations also have germline mutations of one *SMARCB1* allele.[35] Similarly, in utero exposure to topoisomerase inhibitors has been implicated in the development of infant leukemias, which are also

promoted by the RAG1/2 DNA recombinase.[36] Expression of endogenous retroviruses and transposons may also be linked with pathogenesis and therapeutic response at least in some cancers.[37] The interaction among the activity of developmental mutators, environmental exposures, and inherited or constitutional predisposition can also explain the variation in cancer risk among different tissues.[38,39] A precise understanding of the mechanisms that regulate the activity of developmental mutators in early-onset cancers, their environmental mutagens and oncogenic pathogens, and the inherited or constitutional cancer predisposing alleles that may influence their susceptibility should clarify future strategies for their treatment, screening, and potential prevention.

ACKNOWLEDGMENTS

I thank Shweta Bansil for help with SEER data analysis, and Steve Frank, Alejandro Gutierrez, Michael Walsh, and anonymous reviewers for helpful comments. This work was supported by the National Cancer Institute (R01 CA214812), St. Baldrick's Foundation, Damon Runyon-Richard Lumsden Foundation, Burroughs Wellcome Fund, Rita Allen Foundation, and Leukemia and Lymphoma Society.

ORCID

Alex Kentsis https://orcid.org/0000-0002-8063-9191

REFERENCES

1. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*. 1971;68(4):820-823.
2. Strahm B, Malkin D. Hereditary cancer predisposition in children: genetic basis and clinical implications. *Int J Cancer*. 2006;119(9):2001-2006.
3. Foulkes WD. Inherited susceptibility to common cancers. *N Engl J Med*. 2008;359(20):2143-2153.
4. Ripperger T, Bielack SS, Borkhardt A, et al. Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. *Am J Med Genet A*. 2017;173(4):1017-1037.
5. Mandelker D, Zhang L, Kemel Y, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. *JAMA*. 2017;318(9):825-835.
6. O'Driscoll M. Diseases associated with defective responses to DNA damage. *Cold Spring Harb Perspect Biol*. 2012;4(12).
7. Keijzers G, Bakula D, Scheibye-Knudsen M. Monogenic diseases of DNA repair. *N Engl J Med*. 2017;377(19):1868-1876.
8. Zhang J, Walsh MF, Wu G, et al. Germline mutations in predisposition genes in pediatric cancer. *N Engl J Med*. 2015;373(24):2336-2346.
9. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375(5):443-453.
10. Sun J, Meng H, Yao L, et al. Germline mutations in cancer susceptibility genes in a large series of unselected breast cancer patients. *Clin Cancer Res*. 2017;23(20):6113-6119.
11. Brodeur GM, Nichols KE, Plon SE, Schiffman JD, Malkin D. Pediatric cancer predisposition and surveillance: an overview, and a tribute to Alfred G. Knudson Jr. *Clin Cancer Res*. 2017;23(11):e1-e5.
12. Waszak SM, Northcott PA, Buchhalter I, et al. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. *Lancet Oncol*. 2018;19(6):785-798.
13. Ballinger ML, Goode DL, Ray-Coquard I, et al. Monogenic and polygenic determinants of sarcoma risk: an international genetic study. *Lancet Oncol*. 2016;17(9):1261-1271.
14. Malkin D, Nichols KE, Schiffman JD, Plon SE, Brodeur GM. The future of surveillance in the context of cancer predisposition: through the murky looking glass. *Clin Cancer Res*. 2017;23(21):e133-e137.
15. Bullman S, Pedamallu CS, Sicinska E, et al. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. *Science*. 2017;358(6369):1443-1448.
16. Armitage P, Doll R. A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. *Br J Cancer*. 1957;11(2):161-169.
17. Hornsby C, Page KM, Tomlinson IP. What can we learn from the population incidence of cancer? Armitage and Doll revisited. *Lancet Oncol*. 2007;8(11):1030-1038.
18. Kentsis A, Frank SA. Developmental mutators and early onset cancer. *Front Pediatr*. 2020. https://doi.org/10.3389/fped.2020.00189.
19. Papaemmanuil E, Rapado I, Li Y, et al. RAG-mediated recombination is the predominant driver of oncogenic rearrangement in ETV6-RUNX1 acute lymphoblastic leukemia. *Nat Genet*. 2014;46(2):116-125.
20. Mullighan CG, Phillips LA, Su X, et al. Genomic analysis of the clonal origins of relapsed acute lymphoblastic leukemia. *Science*. 2008;322(5906):1377-1380.
21. Swaminathan S, Klemm L, Park E, et al. Mechanisms of clonal evolution in childhood acute lymphoblastic leukemia. *Nat Immunol*. 2015;16(7):766-774.
22. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. *Nat Rev Cancer*. 2018;18(8):471-484.
23. Martin-Lorenzo A, Hauer J, Vicente-Duenas C, et al. Infection exposure is a causal factor in B-cell precursor acute lymphoblastic leukemia as a result of Pax5-inherited susceptibility. *Cancer Discov*. 2015;5(12):1328-1343.
24. Burns MB, Temiz NA, Harris RS. Evidence for APOBEC3B mutagenesis in multiple human cancers. *Nat Genet*. 2013;45(9):977-983.
25. Pettersen HS, Galashevskaya A, Doseth B, et al. AID expression in B-cell lymphomas causes accumulation of genomic uracil and a distinct AID mutational signature. *DNA Repair (Amst)*. 2015;25:60-71.
26. Henssen AG, Kentsis A. Emerging functions of DNA transposases and oncogenic mutators in childhood cancer development. *JCI Insight*. 2018;3(20):e123172.
27. Mack SC, Suzuki H, Taylor MD. Transposase-driven rearrangements in human tumors. *Nat Genet*. 2017;49(7):975-977.
28. Henssen AG, Henaff E, Jiang E, et al. Genomic DNA transposition induced by human PGBD5. *eLife*. 2015;4:e10565.
29. Henssen AG, Koche R, Zhuang J, et al. PGBD5 promotes site-specific oncogenic mutations in human tumors. *Nat Genet*. 2017;49(7):1005-1014.
30. Henssen AG, Reed C, Jiang E, et al. Therapeutic targeting of PGBD5-induced DNA repair dependency in pediatric solid tumors. *Sci Transl Med*. 2017;9(414):eaam9078.
31. Filbin M, Monje M. Developmental origins and emerging therapeutic opportunities for childhood cancer. *Nat Med*. 2019;25(3):367-376.
32. Grobner SN, Worst BC, Weischenfeldt J, et al. The landscape of genomic alterations across childhood cancers. *Nature*. 2018;555(7696):321-327.
33. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. *Nature*. 2013;500(7463):415-421.
34. Alexandrov LB, Kim J, Haradhvala NJ, et al. The repertoire of mutational signatures in human cancer. *bioRxiv*. 2019.
35. Eaton KW, Tooke LS, Wainwright LM, Judkins AR, Biegel JA. Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors. *Pediatr Blood Cancer*. 2011;56(1):7-15.

36. Pendleton M, Lindsey RH, Jr, Felix CA, Grimwade D, Osheroff N. Topoisomerase II and leukemia. *Ann N Y Acad Sci*. 2014;1310:98-110.
37. Rooney MS, Shukla SA, Wu CJ, Getz G, Hacohen N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell*. 2015;160(1-2):48-61.
38. Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science*. 2015;347(6217):78-81.
39. Tomasetti C, Li L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science*. 2017;355(6331):1330-1334.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Kentsis A. Why do young people get cancer? *Pediatr Blood Cancer*. 2020;e28335. https://doi.org/10.1002/pbc.28335