JNP

An Update: Genetic Mutations and Childhood Cancers

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ABSTRACT

Cancer is a disease that arises from genetic mutations that are environmental, inherited, or random in nature. Improvements in technology with next-generation sequencing have made genetic testing and mutation profiling more accessible. It is possible to understand what drives cancerous cell growth and, in some cases, target therapy specifically to those mutations. This article reviews the pathways that can lead to cancer formation, the types of genes involved, options for genetic sequencing, and the role of the nurse practitioner in keeping patients and families informed.

Keywords: cancer, gene, mutation, pediatric

CLINICAL VIGNETTE

A 7-month-old infant was brought to her primary care provider with the chief complaint of refusal to eat, projectile vomiting, and weight loss. An abdominal mass was found on physical exam, leading the primary care provider to refer the family to a pediatric oncologist. Computed tomography scan of the abdomen revealed a retroperitoneal mass arising from the right kidney. Bilateral bone marrow biopsies were performed, excluding metastatic disease. The tumor was surgically resected and both ipsilateral lymph nodes were positive for disease. The patient was diagnosed with Stage 2B neuroblastoma. A biopsy of the tumor was sent out for genomic sequencing, and the tumor came back *MYC* amplified.

AN UPDATE: GENETIC MUTATIONS AND CHILDHOOD CANCERS

Genetics influence the development of cancer. As cells divide they reproduce the genetic information that guides basic cell function, including future reproduction and cell death. Cell division is a tightly controlled process. However, sometimes errors occur leading to mutations. These mutations can be inherited, occur through environmental exposure, or be spontaneous in nature. These changes include inactivation, overexpression, or the production of defective proteins. When mutations occur, the natural pathways found in healthy cells can be subverted, leading to a growth advantage over healthy cells. Cancer develops when mutations lead to uncontrolled cell division, unhindered by the preventative pathways found in healthy cells. This uncontrolled growth leads to tumor formation. Technology has made it possible to assess where mutations are occurring in the genome. In some instances, the mutations and the pathways they leverage provide targets for therapeutic interventions. This article reviews the pathways that can lead to cancer formation, the types of genes involved, options for genetic sequencing, and the role of the nurse practitioner (NP) in keeping patients and families informed. Please see Table 1 for a glossary of terms used in this article.

PATHWAYS TO CANCER

While cancers contain thousands of gene variations, approximately 200 are believed to be responsible for controlling tumorigenesis.[1] These mutations are the "drivers" for common cancers; all other mutations believed to be "passengers" do not provide the cancerous cells with a growth advantage over the healthy cells.[2] According to Vogelstein et al,[2] the driver genes can be classified into 12 signaling pathways that can be further organized into three cellular processes: cell fate, cell survival, and genomic maintenance. If these processes are interrupted the

Table 1. Glossary of Terms

Allele	one of two (or more) versions of a gene
Angiogenesis	the formation of new blood vessels
Apoptosis	programmed/planned cell death
Chromosome	threadlike structure made up of DNA
Differentiation	process by which a cell changes from one type of cell to another, often more specialized, type of cell
DNA	self-replicating material that carries genetic information
Embryogenesis	formation and development of an embryo
Exome	expressed genes in a genome
Gene	region of DNA that acts as instructions to make proteins, basic unit of heredity
Genome	complete set of genetic material found in a cell/organism
Locus	location where a gene is found on the chromosome
Metastasis	development of secondary malignant growths away from the primary site of cancer
Mutation	permanent alteration to the DNA sequence that comprises a gene
Neuroblastoma	type of cancer that forms in certain types of nerve tissue, often found on the adrenal glands
Prognosis	likely outcome of a disease
Protein	provide structure, function, and regulation of the body's tissues and organs
Stem cell	an undifferentiated cell that can indefinitely give rise to more cells of the same type or differentiate into other kinds of cell

Data from Kliegman et al[3]

cancerous cell receives a growth advantage, allowing it to proliferate beyond the capability of a healthy cell.

Cell Fate

Cell fate is determined when the stem cells differentiate into the specialized forms needed to populate various tissues.[4] Stem cells are undifferentiated cells that have the ability to proliferate indefinitely, an important part of embryogenesis.[4] Once differentiated, cells do not divide like stem cells, and they eventually die.[5] Alterations in genes like *APC* (see Table 2 for clarification of genes and associated diagnoses) can overcome the processes that hold differentiated cells in check.[2] This provides a selective growth advantage to those cells, allowing them to divide indefinitely (Tables 3 and 4).

Cell Survival

Some mutations allow for cancer cells to survive more easily. Mutations in *RAS* and *PTEN* genes confer the ability for cells to grow in environments that have limited nutrients.[2] Genes such as *CDKN2A* and *MYC* regulate apoptosis, and mutations in these genes can prevent natural cell death.[6] Tumors that have mutations in *VHL* secrete vascular endothelial growth factor, stimulating angiogenesis to the site of the cancerous cells.[7] These genetic alterations allow mutated cells to survive in conditions where healthy cells cannot.

Genomic Maintenance

During cellular division DNA needs to be replicated. When mistakes occur during the replication process, there are checkpoints where corrections are made or steps are taken to prevent the cells from dividing again.[8] Mutations in genes such as *ATM* and *TP53* breakdown these protective measures.[2] By preventing normal genomic maintenance, the cancer cells are able to continue dividing. Each replication includes the initial mutation and that initial genetic alteration predisposes the cells to additional