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Essential
PEDIATRIC ONCOLOGY





Rakesh Mondal

Forewords
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4 Cytogenetics in Pediatric Cancers

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INTRODUCTION

It has been recognized for quite some time now that genetic factors contribute to the development of a number of human cancers. These factors may be particularly important in the etiology of pediatric malignancies because, in most cases, these young patients have been minimally exposed to environmental mutagens and carcinogens. For example, certain hereditary disorders, such as neurofibromatosis and immunodeficiency, predispose the host to specific childhood cancers. Likewise, certain constitutional chromosomal abnormalities, chromosomal breakage syndromes and defects in DNA repair are associated with increased risk for cancer in these children. There are solid tumors like retinoblastoma and Wilm's tumor, which occur in a hereditary form. Over the past decades great strides have been made towards elucidating the cytogenetic mechanisms involved in carcinogenesis.

Genetic factors play an important role in the development of some pediatric cancers. These factors are more predominant in the pediatric age group because environmental exposures have been minimal. Several pediatric solid tumors, including retinoblastoma and Wilms' tumor, are hereditary. Specific constitutional chromosome abnormalities have been found in these patients which may explain tumorigenesis in some of them. Molecular genetic studies have provided insight into the events occurring at the DNA level in these gene regions. The role of genetics in other sporadic pediatric malignancies are elucidated today as specific chromosome abnormalities are being discovered in the malignant cells of these karyotypically normal individuals now. Certain hereditary disorders, such as neurofibromatosis and immunodeficiency, predispose the host to specific childhood cancers. Likewise, certain constitutional chromosome abnormalities, chromosomal breakage syndromes and DNA repair defects are associated with an increased risk for cancer in children. Technical advances in cytogenetics have made it possible to define specific constitutional and acquired chromosome abnormalities that are associated with specific cancers, thus implicating certain gene regions as being involved in the process of malignant transformation. The rapidly progressing field of molecular genetics is providing further insight into the events occurring at the DNA level in these gene region.

BASIC GENETICS

Between 2 to 5% of all liveborn infants have genetic disorders or congenital malformations. Many diseases in adult life also have a considerable genetic predisposition, including cancer or diabetes.

Classification of Genetic Disorders

A. Traditional modes of inheritance
   - I. Mendelian (Single Gene) disorders
     - i. Autosomal dominant (AD)
     - ii. Autosomal recessive (AR)
     - iii. X-linked recessive (XLR)
     - iv. X-linked dominant (XLD
   - II. Chromosomal disorders
     - i. Numerical abnormalities
     - ii. Structural abnormalities
   - III. Multifactorial disorders

B. Non-traditional modes of inheritance
   - I. Mosaicism
   - II. Genomic imprinting
   - III. Uniparental disomy (UPD)
   - IV. Inheritance of unstable mutations
   - V. Cytoplasmic/mitochondrial inheritance

Chromosomal Disorders

The autosomes are divided in 7 groups according to the position of centromere.

Group A – Chromosome Pairs 1, 2, 3
Group B – Chromosome Pairs 4, 5
Group C – Chromosome Pairs 6, 7, 8, 9, 10, 11, 12
Group D – Chromosome Pairs 13, 14, 15
Group E – Chromosome Pairs 16, 17, 18
Group F – Chromosome Pairs 19, 20
Group G – Chromosome Pairs 21, 22

Each chromosome has a short arm designated as 'p' and a long arm 'q', the arms are joined together at a constriction called centromere 'c'. The types of chromosomes are metacentric (centromere in the middle), submetacentric (centromere towards short arm) and acrocentric (with secondary constriction and satellites). The majority of chromosomal disorders have a low risk of recurrence in the family. 4.5% of stillbirths and 0.6% of live borns have chromosomal abnormalities—numerical or structural. These abnormalities have a close relationship to development of neoplasia.

Numerical Abnormalities

A cell with exact multiple of the haploid number, e.g. 46, 69 is referred to as 'euploid'. Euploid cells with more than the normal diploid number of 46 is called 'polyploid'. Cells deviating from euploid number is 'aneuploid'. The presence of one additional chromosome to the normal homologous pair is called 'trisomy'. A chromosomal number one less than the diploid number is called 'monosomy'. An individual with two or more cell lines are called 'mosaic'.

Structural Abnormalities

Translocation: The transfer of all or part of a chromosome to another non-homologous chromosome, usually through a reciprocal event during meiosis. It can be:
Balanced: In which a full complement of genetic material is present. There is risk of offspring inheriting an unbalanced form in next generation.
Unbalanced: Here, due to deletion or duplication, full complement of genetic material is not present. This may result in spontaneous abortions or multiple physical/mental defects.
Robertsonian: This is translocation of 2 aerocentric chromosomes, in which, the small fragment formed by 2 short armed is usually lost.
Deletion: This is loss of portion of a chromosome, either terminal (5p-) or middle portion, i.e. interstitial (11p-)
Fragile site: Constriction sites other than centromere is known as fragile site which shows a tendency to break, e.g. Fragile X syndrome.
Duplication: It is presence of two copies of a segment of chromosome. It arises by unequal crossing over during meiosis.
Inversion: This is reverse joining of portion of a chromosome. This can be pericentric (on either side of centromere, involving both arms) or paracentric (on one side of centromere, in one arm only) e.g. 9q.
Ring chromosome: Both arms joining at terminal portion with loss of fragments to give a ring-like appearance, e.g. ring chromosome 18.
Contiguous gene syndrome: This involves microdeletion or microduplication resulting in involvement of genes that are adjacent to each other on a chromosome.

Somatic Cell Mutation

Some cancers can be inherited as simple Mendelian traits, with clear patterns of transmission. But though most cancers involve quite substantial changes in the genetic material, such mutations are somatic and there is no risk to further generations.

Mosaicism

Mosaicism is presence of two or more genetically different cell lines. Phenotype expression in mosaicism depends on dosage-affect relationship. It occurs as a postzygotic event and can be:

Chromosomal Mechanism

It has been recognized in cultured lymphocytes of patients with aneuploidy, e.g. Down syndrome, Turner syndrome, Diploid/Triploid phenotype, Pallister-Killian (12p isochromosome) syndrome, hypomelanosis of Ito.

Single Gene Mosaicism

Isomatic mosaicism for single gene mutation, e.g. Maccune-Albright syndrome.

Germline Mosaicism

Presence of mosaicism in germ cells, e.g. found in DMD, chronic granulomatous disease.

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Genomic Imprinting

This means that the level of expression of the genes depends on the parent of origion. The genes are modified during gametogenesis and as a result are activated or inactivated. Deletion in chromosome 15q 11 or 13 region results in Prader-Willi syndrome, if inherited from father and in Angelman's syndrome, it inherited from mother. Other examples include Beckwith-Wiedeman syndrome and transient neonatal diabetes mellitus.

Uniparental Disomy

An individual may inherit both homologous chromosomes from only one of his parents. Thus a father with hemophilia can have an affected son and a child with cystic fibrosis may be born to a couple in which only the mother was carrier.

Unstable Mutation

Also known as Triplet Nucleotide Repeats. Fragile X mutations consists of an increase in the size of region in fragile X mental retardation (FMR-I) gene. This region contains a long CGG trinucleotide repeat sequence. In normal persons there are between 10–15 copies of this repeat and this is inherited in stable fashion. A small increase between 50–200 makes this sequence unstable, a condition known as premutation. A man carrying premutation is a 'normal transmitting male'. If this reaches a critical size of greater than 200 CGG triplets, it becomes a full mutation. Unstable mutations also reported in myotonic dystrophy, Huntigton's chorea and Kennedy's disease.

Mutations

A mutation may be defined as a detectable and heritable change in genetic material that is not caused by genetic recombination, a permanent change in the DNA. Mutations that affect germ cells are transmitted to the progeny giving rise to inherited diseases. Somatic cell mutations, though do not cause hereditary diseases, but are very important in the genesis of cancers and congenital malformations. Based on the extent of genetic changes, mutations have been classified into three categories.

Genome Mutation

This involves loss or gain of whole chromosomes, giving rise to monosomy or trisomy, i.e. numerical changes.

Chromosome Mutation

This results from rearrangement of genetic material and gives rise to structural changes in the chromosome.

These two mutations are transmitted only infrequently, because most are incompatible with survival. The vast majority of mutations associated with hereditary diseases are submicroscopic gene mutation. These may result in partial or complete deletion, substitution or insertion of a gene or more often a single nucleotide base. Mutation involving a single nucleotide base is termed a point mutation.

Point Mutation within Coding Sequences

There are different types:

Silent mutation: Mutation results in a different codon but the amino acid coded is the same as that of the original codon.

Missense mutation: Mutation results in coding of a new amino acid in place of the original resulting in production of an abnormal protein. If the substituted amino acid causes little change in the function of the protein, the mutation is called a conservative missense mutation. But, if the normal amino acid is replaced by a totally different one, it is called a non-conservative missense mutation, e.g. sickle mutation. The nucleotide triplet GAG codes for glutamic acid in β-globin chain of normal hemoglobin. In sickle cell anemia, this triplet is changed to GTG, which codes for valine, resulting in abnormal hemoglobin.

Nonsense mutation: Mutation results in introduction of a stop codon causing premature termination of protein synthesis resulting in a truncated protein. In β-globin, a pint mutation affecting the codon for glutamine (CAG) creates a stop codon UAG, if U substitutes C. This leads to premature termination of β-globin gene translation, resulting in β°-thalassemia.

Frame-shift mutation: Mutation causing single-base insertion or deletion resulting in a shift of the translational reading frame which leads to production of a completely different sequence of amino acids. Singe base deletion at ABO locus leading to frame-shift mutation in A allele can lead to O allele.

Point Mutation with Non-coding Sequences

Mutations in promoter region and introns can result in abnormal production, i.e. in excess or less. Mutation in

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exon/intron boundary may lead to differently spliced mRNA.

Polymorphisms

Some germline mutations occur in frequency of more than 1% in general population, which mostly have no relevance in health or disease. These are called polymorphisms and they may help in the process of evolution.

Protective Mutation

Uncommonly, mutations may be protective. HIV uses a chemokine receptor CCR5, to enter cells. A deletion in the CCR5 gene can protect from HIV infection.

Mutagens

Mutations may be generated spontaneously by rare errors that occur during DNA replications. More frequently mutations are produced by exposure to certain agents called mutagens, like high energy radiation (e.g. X-ray, U-V rays, γ-rays), certain viral infections (E-B virus, Herpes simplex, HPV, Coxsackie B) and certain chemicals (arsenic, asbestos, benzene, cadmium, ethylene oxide), etc.

Gain-of-function Mutation

This can result in an increase in the ability of a protein molecule to perform one or more normal functions or in overexpression of a gene product. Most frequently they produce autosomal dominant disorders as in achondroplasia or Charcot-Marie-Tooth disease, type-IA.

Loss-of-function Mutation

They are frequently observed in autosomal recessive disorders in which loss of 50% enzyme activity in the heterozygote continued to allow for normal function. They can have a dominant negative effect when the abnormal protein product activity interferes with the function of the normal protein product. Loss-of-function mutations can result in conditions in which 50% of the gene product is insufficient for normal function. This is termed as haploinsufficiency.

Genetic disorders are far more common than widely appreciated. The lifetime frequency of genetic diseases is estimated to be 670 per 1000. Included in this figure are not only the "classic" genetic disorders, but also cancer, diabetes or cardiovascular diseases.

A neoplasm is defined as an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissue and persists in the same excessive manner after cessation of the stimuli which evoked the change. The persistence of growth, even after withdrawal of the inciting stimulus, results from heritable genetic alterations that are passed down to the progeny of the tumor cells. These genetic changes allow excessive and unregulated proliferation that becomes autonomous. The entire population of cells within a tumor arises from a single cell, that has incurred genetic change, and hence the growth is said to be clonal. Certain anatomic features suggest the benign nature of a growth, while others point towards a malignant potential. Differentiation refers to the extent to which neoplastic cells resemble comparable normal cells, both morphologically and functionally. Lack of differentiations is called anaplasia. Anaplasia is marked by several morphologic changes. Both the cells and the nuclei characteristically display variation in size and shape, which is called pleomorphism. The nuclei contain an abundance of DNA and are extremely dark-staining, i.e. hyperchromatic. The nuclei are disproportionately large, and the nucleus to cytoplasm ratio may approach 1:1, instead of normal 1:4 to 1:6. Undifferentiated tumors usually possess large numbers of mitoses, reflecting the higher proliferative activity. Thus, malignant cells show atypical, bizarre mitotic figures, sometimes producing tripolar, quadripolar or multipolar spindles. The orientation of anaplastic cells is markedly disturbed, i.e. there is loss of normal polarity. Another important feature of anaplasia is the formation of tumor giant cell, some possessing a single huge polymorphic nucleus and other having two or more nuclei. Some anaplastic growths have scanty vascular stroma, and there are large central areas of ischemic necrosis. Dysplasia means disordered growth, which is mainly encountered in epithelia, and is characterized by constellation of changes that include a loss in the uniformity of individual cells as well as their architectural orientation.

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GENETIC PREDISPOSITION TO CANCER

For a large number of cancer types, there exist not only environmental influences, but also genetic predispositions. Lung cancer is related to cigarette smoking, yet mortality from lung cancer has been shown to be four times greater among non-smoking relatives of lung cancer patients than among non-smoking relatives of smoker controls. Genetic predisposition to cancer have been divided into three categories:

Autosomal Dominant Inherited Cancer Syndromes

There are several well-defined cancers in which inheritance of a single mutant gene greatly increases the risk of developing a tumor. Usually, this is a point mutation occurring in a single allele of a tumor suppressor gene. The defect in the second allele occurs in the somatic cells, as a consequence of chromosome deletion. This is the classic two-mutation hypothesis of Knudson. Childhood retinoblastoma is the most striking example in this category. Approximately 40% of retinoblastomas are hereditary. Carriers of a mutant of RB tumor suppressor gene have a 10,000-fold increased risk of developing the tumor. The D group chromosome involved in all cases is chromosome 13, and the band common to all the deletions is 13q14. These data suggest that the retinoblastoma gene is located within this chromosomal band. Gene dosage studies have demonstrated that the locus for the enzyme esterase D is also located in band I 3q 14, and is closely linked to the retinoblastoma gene 13. Thus, there is a biochemical marker for small deletions of this region of chromosome 13. Most of the patients with this specific chromosomal deletion have other phenotypic abnormalities in addition to retinoblastoma. Although there is no classical phenotype, developmental delay, microcephaly, microphthalmia, and skeletal and genitourinary malformations have been reported. There is also an increased risk for the development of a second primary malignancy, usually an osteogenic sarcoma, both within and outside the field of radiation therapy. Again, individuals who inherit the autosomal dominant mutation of adenomatous polyposis coli (APC) tumor suppressor gene, have innumerable polypoid adenomatous growth of colon, virtually 100% of which are fated to develop a carcinoma later. Other examples in this category are Li-Fraumeni syndrome resulting from germline mutation of p53 gene, multiple endocrine neoplasia (MEN-1 and 2), hereditary nonpolyposis colonic cancer. Both incomplete penetrance and variable expressivity occur here like other autosomal dominant conditions. Neurofibromatosis has been linked to NF-1 and NF-2 genes. Deletion in short arm of chromosome 11 is associated with Wilms' tumor.

Common Features of Hereditary Cancers

a. High incidence of same or related tumors among family members
b. Bilateral involvement of organs
c. Multiple primary malignant neoplasms
d. Early age of onset with minimal exposure to environmental carcinogens
e. Autosomal dominant inheritance pattern.

Defective DNA Repair Syndromes

These conditions generally have an autosomal recessive pattern of inheritance. They are characterized by defects in DNA repair and resultant DNA instability. Included in this group are xeroderma pigmentosum, ataxia-telangiectasia and bloom syndrome. Hereditary non-polypoid colon cancer (HNPCC), although an autosomal dominant condition, may be included in this category. This is caused by inactivation of a DNA mismatch repair gene.

Familial Cancers

Virtually all the common types of cancers that occur sporadically have also been reported to occur in familial forms, without any clearly defined pattern of transmission. Examples included carcinomas of colon, breast, ovary, brain and melanoma. Two breast cancer susceptibility genes, namely BRCA-1 and BRCA-2 have been identified. Mutation of p16INK4A tumor suppressor gene has been linked to familial melanomas.

Molecular Basis of Cancer (Flow chart 4.1)

There are some fundamental points regarding the molecular basis of cancers and carcinogenesis. The most important are listed below:

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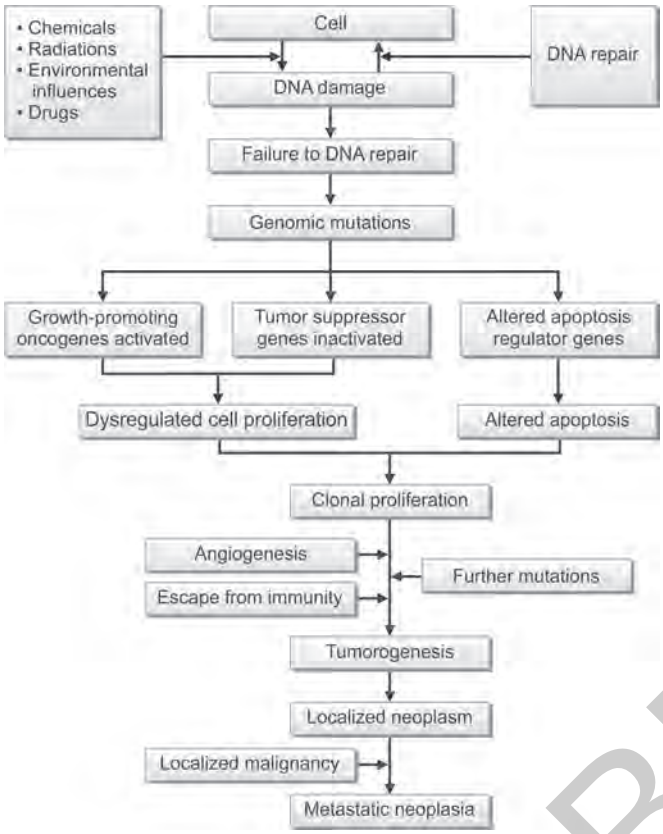
Flow chart 4.1: Schematic diagram showing oncogenesis



Nonlethal genetic damage: This lies at the heart of carcinogenesis. Such damage may be inherited through germline or may be acquired by external agents, e.g. chemicals, radiation or viruses. Some mutations may even be spontaneous, without any detectable insults.

Clonal expression of a single precursor cell: Tumors are mostly monoclonal. The most commonly used method to determine tumor clonality involves the analysis of methylation pattern adjacent to the highly polymorphic locus of human androgen receptor gene. For neoplasms with a specific translocation, as in myeloid leukemias, the presence of translocation can be used to assess clonality. Immunoglobulin receptor and T-cell receptor gene rearrangements act as markers of clonality in B- and T-cell lymphomas, respectively.

Regulatory genes: There are four classes of normal regularity genes—the growth-promoting protooncogenes, the growth-inhibiting tumor suppressor genes, programmed cell death regulating apoptosis genes and those involved in DNA repair—the DNA repair genes. Mutant alleles of protoancogenes are considered dominant because they transform cells despite the presence of a normal counterpart. In contrast, both normal alleles of the tumor suppressor genes have to be damaged for transformation to occur. So, this family of genes is referred to as recessive oncogenes. But, due to haploinsufficiency some tumor suppressor genes may lose their suppressor activity when a single allele is lost or inactivated.

Mutator phenotype: DNA repair genes affect cell proliferation or survival indirectly by influencing the ability of the organism to repair non-lethal damage in other genes, including proto-oncogenes, tumor suppressor genes and apoptosis genes. A disability in the DNA repair genes can predispose to mutations in the genome and hence to neoplastic transformations. Such propensity to mutations is called mutator phenotype. Both alleles of DNA repair genes must be inactivated to induce such genomic instability.

Tumor progression: Carcinogenesis is a multistep process, at both phenotypic and genetic levels. The phenotypic attributes of a malignant neoplasm, like excessive growth, local invasiveness, distant metastasis, etc. are acquired in a stepwise fashion, a phenomenon called tumor progression.

Essential Alterations for Malignant Transformation

Till date, hundreds of cancer-associated genes have been discovered. Some, such as p53, are commonly mutated. Others, such c-abl, are affected only in certain leukemias. There are certain fundamental changes in the cell physiology that together determine malignant phenotype.

Self-sufficiency in growth signals: Neoplasms have the capacity to proliferate with external stimuli, usually as a consequence of an oncogene activation.

Inability to sense growth-inhibitory signals: Tumors may not respond to signals from growth-inhibitory molecules like transforming growth factor-β (TFG-β) or CDK inhibitors Cip/Kip and INK4/ARF families.

Evasion of apoptosis: Tumors may be resistant to programmed cell death, as a consequence of inactivation of p53 or other genes.

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Defects in DNA repair: Tumors may fail to repair DNA damage caused by carcinogens or unregulated cellular proliferation.

Limitless replicative potential: Malignant cells have unrestricted proliferative capacity, associated with telomere length and function.

Sustained angiogenesis: The vascular supply and angiogenesis are induced by various factors, the most important being vascular endothelial growth factor (VEGF).

Ability to invade and metastasize: This depends on processes that are intrinsic to the cell or are initiated by signals from surrounding tissue.

The orderly progression of cells through the various phases of cell cylce ($G_1 \rightarrow S \rightarrow G_2 \rightarrow M$) is orchestrated by cyclins, cyclin-dependent kinases (CDKs) and by their inhibitors. There are two check-points at G1/S and G2/M transitions. The S phase is the point of no return in cell cycle, and before a cell makes the final commitment to replicate, G1/S checkpoint checks for DNA damage. If DNA damage is present, DNA repair machinery are put in motion. If the damage is not repairable, apoptotic pathways are activated to kill the cell. The G2/M checkpoint monitors the completion of DNA replication and checks whether the cell can safely initiate mitosis and separate sister chromotids. Defects in G2/M checkpoints give rise to chromosomal abnormalities. These checkpoint defect is a major cause of genetic instability in cancer cells. Cell-cycle arrest in both of the checkpoints are mainly mediated by p53, which induces cell cycle inhibitor p21.

Specific chromosomal abnormalities have been identified in most leukemias and lymphomas. Two types of chromosomal rearrangements can activate protooncogenes—translocation and inversion. Translocations are much more common. In lymphoid tumors, specific translocations result in overexpression of protooncogenes by removing them from their regulatory elements. In many hematopoietic neoplasms, the translocations allow normally unrelated sequences from two different chromosomes to recombine and form hybrid genes that encode growth-promoting chimeric proteins. The Philadelphia chromosome, characteristic of CML and subset of ALL, provides the prototypic example of an oncogene formed by fusion of two separate genes. In these cases, a reciprocal translocation between chromosomes 9 and 22 relocates a truncated portion of protooncogene c-ABL (from chromosome 9) to BCR (Breakpoint Cluster Region) on chromosome 22. The hybrid fusion gene BCR-ABL encodes a chimeric protein that has constitutive tyrosine kinase activity leading to activation of multiple pathways. Overexpression of a protooncogene caused by translocation is best exemplified by Burkitt's lymphoma. All such tumors carry one three translocations, each involving chromosome 8q24, where MYC gene has been mapped, as well as one of the three Ig gene-carrying chromosomes. The MYC-containing segment of chromosome 8 is translocated to chromosome 14q band 32 placing it close to Ig heavy-chain (IgH) gene. Transcription factors are often the partners of gene fusion. For instance, the MLL gene on 11q23 is known to be involved in 25 different translocations with different partner genes (Table 4.1). The MLL gene is affected in childhood ALL and ANLL. The Ewing Sarcoma gene (EWS) at 22q12 was first described in t(11;22)(q24;12) reciprocal translocation, but may be found in other types of sarcomas as well.

Reduplication and amplification of DNA sequences may also activate protooncogenes leading to overexpression. Such amplification may produce several

Table 4.1: Translocations and oncogenes

Childhood malignancy	*Translocation*	*Genes*
Acute leukemias (ALL & ANLL)	(4;11)(q21;q23) (6;11)(q27;q23)	AF4 4q21 MLL 11q23 AF6 6q27 MLL 11q23
T-cell ALL	(8;14)(q24;q11) (10;14)(q24;q11)	C-MYC 8q24 TCR-α 14q11 HOX11 10q24 TCR-α 14q11
Burkitt lymphoma	(8;14)(q24;q32)	C-MYC 8q24 IgH 14q32
Follicular lymphoma	(14;18)(q32;q21)	IgH 14q32 BCL-2 18q21
Chronic myeloid leukemia	(9;22)(q43;q11)	ABL 9q34 BCR 22q11
Ewing sarcoma	(11;22)(q24;q12)	FC-1 11q24 EWS 22q12

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hundred copies of the protooncogene in the tumor cell. Two patterns are seen—multiple small, chromosome-like structures called double minutes (dms) and homogeneous staining regions (HSR). The latter derive from the assembly of amplified genes into new chromosomes. In about 30% cases of neuroblastomas, there is amplification of N-MYC genes, present both dms and HSR. Other examples are breast carcinoma (ERB-B2), small cell lung cancer (C-MYC, L-MYC, N-MYC) and squamous cell carcinoma (CYCLIN-D1).

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