# Lecture 10.
# Cytogenetics of tumors

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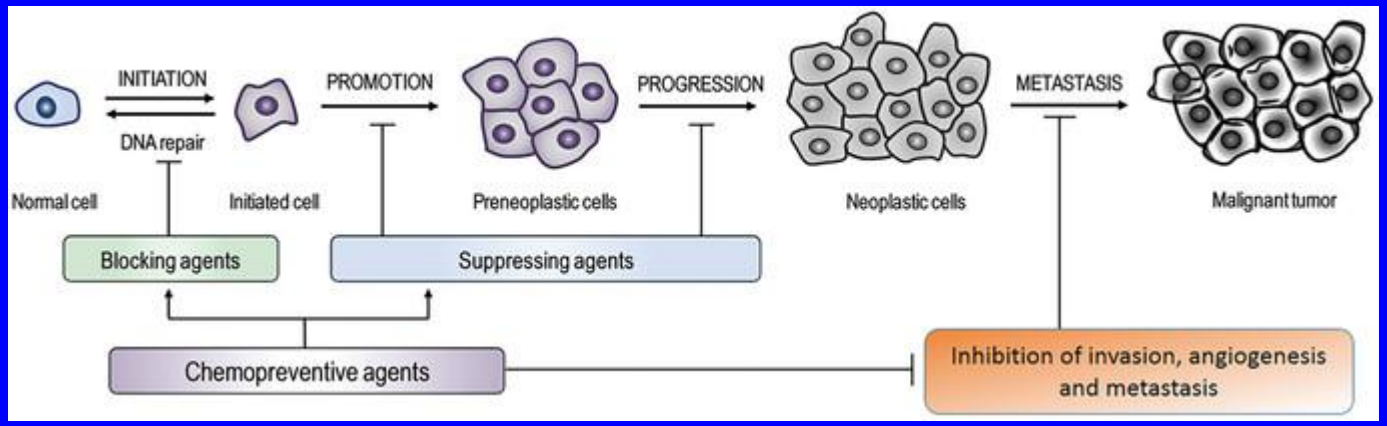
# CANCER

Cancer is a genetic disease that could develop either from a predisposing mutation followed by acquired somatic mutations or from an accumulation of somatic mutations that develop into a cancer phenotype. Many different types of DNA alteration have been reported in cancer, with some of the recognized forms being as follows:

- Subtle DNA or RNA alterations
- DNA methylation
- Changes in chromosome number (aneuploidy)
- Loss of heterozygosity
- Chromosome translocations in somatic cells rather than in germ cells
- Gene amplification
- Incorporation of exogenous sequences

Oncogenes and tumor suppressor genes control cellular proliferation by cell death or cell birth, whereas caretaker genes control the rate of mutation. Cells with defective caretaker genes might acquire mutations in all genes, including oncogenes and tumor suppressor genes.

# CARCINOGENESIS PHASES




***Initiation*** involves the alteration, change, or mutation of genes arising spontaneously or induced by exposure to a carcinogenic agent. Genetic alterations can result in dysregulation of biochemical signaling pathways associated with cellular proliferation, survival, and differentiation.

The ***promotion*** stage is considered to be a relatively lengthy and reversible process in which actively proliferating preneoplastic cells accumulate.

***Progression*** is the phase between a premalignant lesion and the development of invasive cancer. It is the final stage of neoplastic transformation, where genetic and phenotypic changes and cell proliferation occur.

***Metastasis*** involves the spread of cancer cells from the primary site to other parts of the body through the bloodstream or the lymph system.

# CYTOGENETICS OF HEMATOLOGIC NEOPLASMS

Chromosomal translocation plays a major role in the development of hematologic malignancies. About 50% of hematopoietic neoplasms somatically acquire chromosomal translocations, which activate proto-oncogenes in most cases. This could, in turn, disrupt the critical balance of cell proliferation, cell maturation, and cell death. Most chromosomal translocation-induced hematopoietic neoplasms are restricted to a single lineage and, depending on the acquisition of the mutation, are arrested at a particular developmental stage of maturation.

Historically, hematological malignancies have been classified according to morphological phenotype using what is known as the French–American–British (FAB) classification. Since 1995, the European Association for Haematopatholgy and the Society for Haematopathology, in collaboration with many subspecialties, have developed the World Health Organization (WHO) classification.

The new WHO classification of hematologic malignancies stratifies neoplasms primarily according to lineage (e.g., myeloid, lymphoid, histiocytic/dendritic cell, and mast cell). Within each category, neoplasms are further defined by a combination of morphology, immunophenotyping, genetic, and clinical information. The “cell of origin” in this classification is defined as the presenting cell phenotype, because in many cases, particularly in lymphoid disorders, the cell in which the initial transformation occurs is not known. The WHO classification defines tumors as deriving from myeloid and lymphoid tissues.

**Disease Categories According to WHO Classification**

- Chronic Myeloproliferative Diseases (MPDs)
  - Chronic myelogeneous leukemia
  - Chronic neutrophilic leukemia
  - Chronic eosinophilic leukemia and hypereosinophilic syndrome
  - Polycythemia vera
  - Chronic idiopathic myelofibrosis
  - Essential thrombocythemia
  - Myeloproliferative disease, unclassifiable
- Myelodysplastic/Myeloproliferative Diseases
  - Chronic myelomonocytic leukemia (CMML)
  - Atypical chronic myeloid leukemia (aCML)
  - Juvenile myelomonocytic leukemia (JMML)
  - Myelodysplastic/myeloproliferative diseases, unclassifiable
- Myelodysplastic Syndromes (MDSs)
  - Refractory anemia (RA)
  - Refractory anemia with ringed sideroblasts (RARS)
  - Refractory cytopenia with multilineage dysplasia (RCMD)
  - Refractory anemia (MDS) with excess blasts (RAEB)
  - Myelodysplastic syndrome associated with isolated del(5q) chromosome abnormality ("5q– syndrome")
  - Myelodysplastic syndrome, unclassifiable
- Acute Myeloid Leukemia (AML)
  - Acute myeloid leukemia with recurrent cytogenetic abnormalities
    - AML with t(8;21)(q22;q22) *AML1(CBFa)/ETO*) (FAB M2)
    - AML with inv(16)(p13q22) or t(16;16)(p13;q22), *(CBFβ/MYH11)*
    - AML with t(15;17)(q22;q21) (*PML/RARA* and variants thereof) (FAB M3)
    - AML with 11q23 *(MLL)* abnormalities
  - Acute myeloid leukemia with multilineage dysplasia
    - With prior myelodysplastic syndrome
    - Without prior myelodysplastic syndrome
  - Acute myeloid leukemia and myelodysplastic syndrome, therapy-related
    - Alkylating agent related
    - Topoisomerase II inhibitor related
  - Acute myeloid leukemia not otherwise categorized
    - AML, minimally differentiated
    - AML without maturation
    - AML with maturation
    - Acute myelomonocytic leukemia (FAB M4)
    - Acute monoblastic and monocytic leukemia (FAB M5)
    - Acute erythroid leukemia (FAB M6)
    - Acute megakaryoblastic leukemia (FAB M7)
    - Acute basophilic leukemia
    - Acute panmyelosis with myelofibrosis
    - Myeloid sarcoma
  - Acute leukemia of ambiguous lineage
- Precursor B- and T-Cell Neoplasms
  - Precursor B-lymphoblastic leukemia/lymphoma
  - Precursor T-lymphoblastic leukemia/lymphoma
- Mature B-Cell Neoplasms
  - Chronic lymphocytic leukemia/small lymphocytic lymphoma
  - B-Cell prolymphocytic leukemia
  - Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia
  - Splenic marginal zone lymphoma
  - Hairy cell leukemia
  - Plasma cell neoplasms
    - Plasma cell myeloma
    - Plasmacytoma
    - Solitary plasmacytoma of bone
    - Monoclonal immunoglobulin deposition diseases
    - Heavy-chain diseases
  - Extranodal marginal zone B-cell lymphoma (MALT lymphoma)
  - Nodal marginal zone B-cell lymphoma
  - Follicular lymphoma
  - Mantle cell lymphoma
  - Diffuse large B-cell lymphoma
  - Mediastinal (thymic) large B-cell lymphoma
  - Intravascular large B-cell lymphoma
  - Primary effusion lymphoma
  - Burkitt lymphoma/leukemia
  - Lymphomatoid granulomatosis
- Mature T-Cell and NK-Cell Neoplasms
  - T-Cell prolymphocytic leukemia
  - T-Cell large granular lymphocytic leukemia
  - Aggressive NK-cell leukemia
  - Adult T-cell leukemia/lymphoma
  - Extranodal NK/T-cell lymphoma, nasal type
  - Enteropathy-type T-cell lymphoma
  - Hepatosplenic T-cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Blastic NK-cell lymphoma
  - Mycosis fungoides/Sézary syndrome
  - Primary cutaneous CD-30 positive T-cell lymphoproliferative disorders
    - Primary cutaneous anaplastic large cell lymphoma (C-ALCL)
    - Lymphomatoid papulosis
    - Borderline lesions
  - Angioimmunoblastic T-cell lymphoma
  - Peripheral T-cell lymphoma, unspecified
  - Anaplastic large cell lymphoma
- Hodgkin's Lymphoma
  - Nodular lymphocyte predominant Hodgkin's lymphoma
  - Classical Hodgkin'slymphoma
    - Nodular sclerosis Hodgkin'slymphoma
    - Mixed cellular Hodgkin'slymphoma
    - Lymphocyte-rich classical Hodgkin'slymphoma
    - Lymphocyte-depleted Hodgkin'slymphoma
- Immunodeficiency-Associated Lymphoproliferative Disorders
  - Lymphoproliferative diseases associated with primary immune disorders
  - Human immunodeficiency virus-related lymphomas
  - Posttransplant lymphoproliferative disorders
  - Methotrexate-associated lymphoproliferative disorders
- Histiocytic and Dendritic Cell Neoplasms
  - Histiocytic sarcoma
  - Langerhans cell histiocytosis
  - Langerhans cell sarcoma
  - Interdigitating dendritic cell sarcoma/tumor
  - Follicular dendritic cell sarcoma/tumor
  - Follicular dendritic cell sarcoma/tumor
  - Dendritic cell sarcoma, not otherwise specified
- Mastocytosis
  - Cutaneous mastocytosis
  - Systemic mastocytis
  - Mast cell sarcoma
  - Extracutaneous mastocytoma

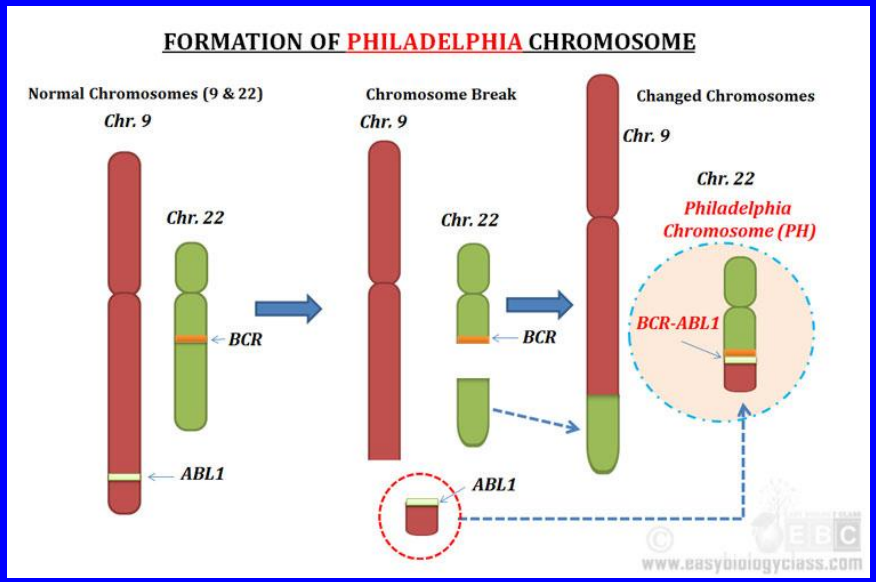
# CHRONIC MYELOPROLIFERATIVE DISEASES (MPDS): CHRONIC MYELOGENOUS LEUKEMIA (CML)

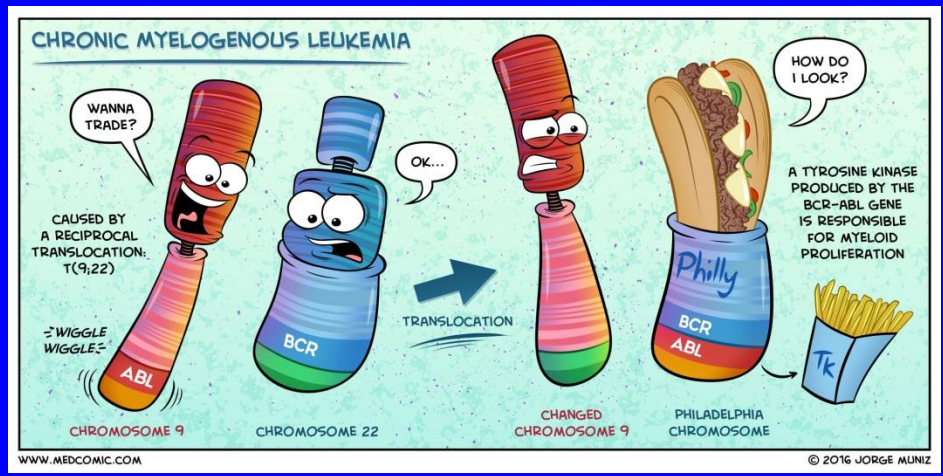
This disorder is characterized by abnormal but effective hematopoiesis, resulting in the proliferation of mature cells, with high peripheral blood levels of one or more cell lines. Chronic myelogenous leukemia is defined as a qualitative disorder originating from two or more cell types with a multilineage phenotype. CML alone accounts for about 15–20% of all cases of leukemia.

The disease can occur at any age, but the most common age of presentation is between the ages of 50 and 59 years. In most cases, it is a triphasic disorder, starting with the chronic phase that, if left untreated, can proceed to a CML-accelerated phase and CML with blast crisis. This disorder is mainly of hematopoietic tissue in origin, involving primarily the blood, bone marrow, spleen, and liver, but during blast crisis, extramedullary tissues, including lymph nodes, skin, soft tissue, and sometimes the central nervous system, can be involved. The most common presenting features of CML are very mild to high white blood cell counts, fatigue, night sweats, and/or splenomegaly.

# CHRONIC MYELOGENOUS LEUKEMIA (CML)

In the WHO classification, the diagnostic criterion for CML is the unequivocal presence of a "Philadelphia" (Ph) rearrangement [t(9;22)(q34;q11.2)], involving the Breakpoint Cluster Region and Ableson oncogenes (BCR and ABL1). Approximately 90–95% of CML patients present with a Philadelphia rearrangement at the time of initial diagnosis.



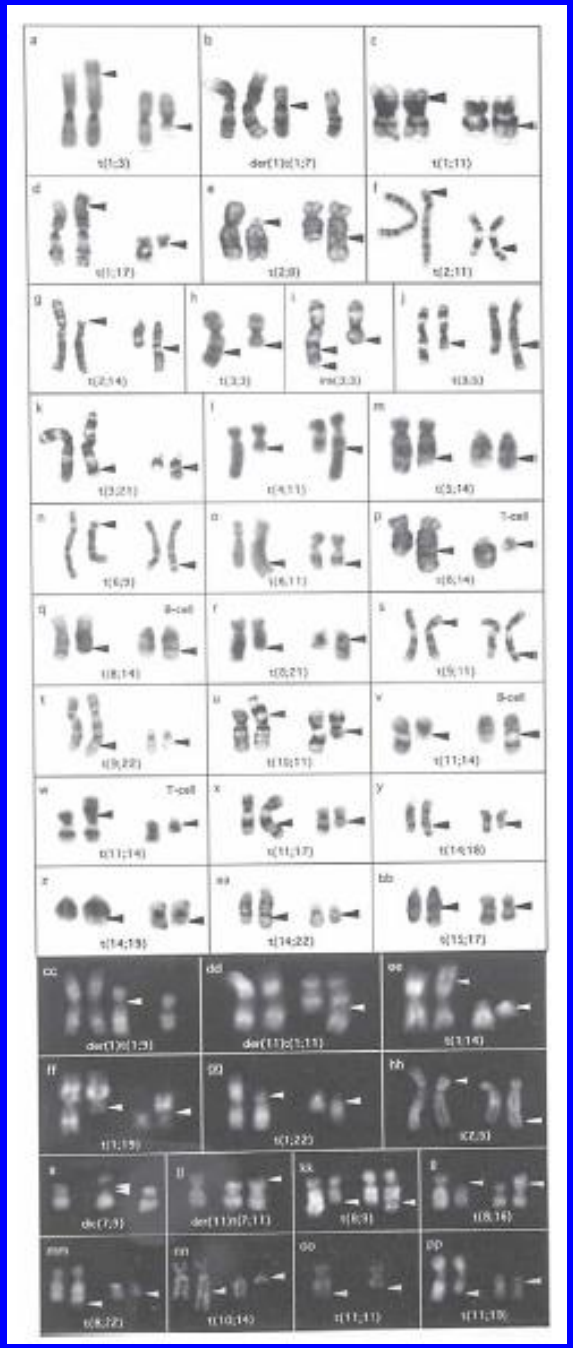
# CHRONIC MYELOGENOUS LEUKEMIA (CML)

Common "major route" cytogenetic changes in CML are trisomy 8, isochromosome 17q, an additional derivative chromosome 22 ("Philadelphia chromosome"), and trisomy 19. Less common "minor route" changes include trisomy 21, loss of the Y chromosome in men, monosomy 7, monosomy or trisomy 17, and a (3;21) translocation. Patients often present with unique or "patient-specific" secondary changes. These all have some role to play in transformation to blast crisis and in prognosis.

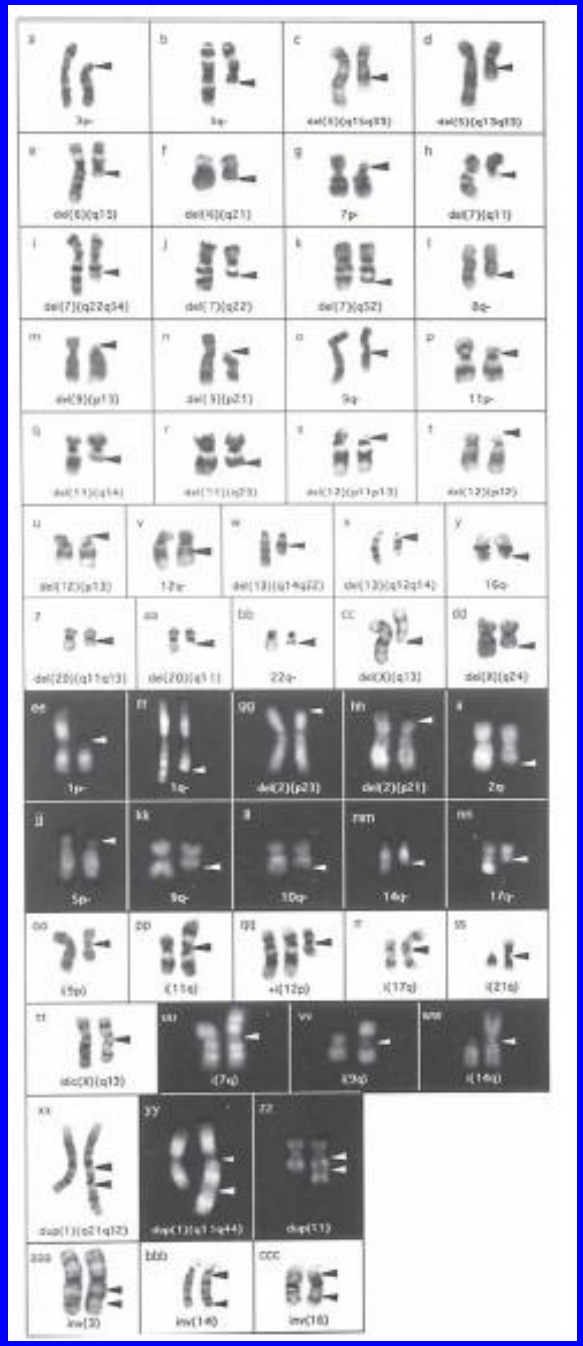
**Major Routes of Cytogenetic Evolution in CML Blast Crisis**

| Additional change | Frequency (%) |
|---|---|
| +Ph[a] | 15 |
| i(17q) | 12 |
| +8 | 11 |
| +Ph, +8 | 8 |
| +8,i(17q) | 7 |
| +Ph,+8,+19 | 5 |
| +Ph,+19 | 4 |
| +8,+19 | 2 |
| +Ph,+8,i(17q) | 2 |
| +19 | 1 |
| i(17q),+Ph | 1 |
| +8,i(17q),+19 | 1 |
| +Ph,+8,i(17q), +19 | 1 |
| i(17q),+19 | >1 |
| i(17q),+19, +Ph | >1 |

[a] +der(22)t(9;22)(q34.1;q11.2).



Translocations seen in hematologic disorders



Isochromosomes duplications and deletions seen inhematologic disorders

# CYTOGENETICS OF SOLID TUMORS

Aspects of the cytogenetic approach present unique challenges in solid tumors:

1) solid tumors are generally karyotyped using specimens obtained by open biopsy. Therefore, solid-tumor cytogenetic analyses are typically performed at the time of initial diagnosis or when the tumor is rebiopsied at the time of clinical progression, but they are not performed routinely to monitor treatment response in a given patient. I

2) Solid-tumor karyotypes are often extremely complex, particularly those in highly malignant solid tumors. A single metaphase cell might contain dozens of clonal and nonclonal chromosomal aberrations, and in such tumors, it is impractical to characterize the exact mechanisms of rearrangement responsible for each chromosomal aberration, particularly in the course of a routine clinical analysis.

3) The solid-tumor sample generally must be disaggregated by mechanical and enzymatic methods before the cells are placed in tissue culture.

**Typical Cytogenetic Aberrations In Soft Tissue and Bone Tumors**

| Histologic findings | Characteristic cytogenetic events | Molecular events | Frequency | Diagnostic utility? |
|---|---|---|---|---|
| Alveolar soft part sarcoma | t(X;17)(p11.2;q25) | *ASPL-TFE3* fusion | >90% | Yes |
| Aneurysmal bone cyst (extraosseous) | 16q22 and 17p13 rearrangements | | >50% | Yes |
| Angiomatoid fibrous histiocytoma | t(12;16)(q13;p11.2) | *FUS-ATF1* fusion | | |
| Chondromyoxid fibroma | Deletion of 6q | | >75% | Yes |
| Chondrosarcoma | | | | |
| Skeletal | Complex* | | >75% | ? |
| Extraskeletal myxoid | t(9;22)(q22;q12) | *EWS-NR4A3* fusion | >75% | Yes |
| | t(9;17)(q22;q11) | *TAF2N-NR4A3* fusion | <10% | Yes |
| | t(9;15)(q22;q21) | *TCF12-NR4A3* fusion | <10% | Yes |
| Clear cell sarcoma | t(12;22)(q13;q12) | *EWS-ATF1* fusion | >75% | Yes |
| Desmoplastic small round cell tumor | t(11;22)(p13;q12) | *EWS-WT1* fusion | >75% | Yes |
| Dermatofibrosarcoma protuberans | Ring form of chromosomes 17 and 22 | *COL1A1-PDGFB* fusion | >75% | Yes |
| | t(17;22)(q21;q13) | *COL1A1-PDGFB* fusion | 10% | Yes |
| Endometrial stromal tumor | t(7;17)(p15;q21) | *JAZF1-JJAZ1* | 30% | Yes |
| Ewing's sarcoma | t(11;22)(q24;q12) | *EWS-FLI1* fusion | >80% | Yes |
| | t(21;22)(q12;q12) | *EWS-ERG* fusion | 5–10% | Yes |
| | t(2;22)(q33;q12) | *EWS-FEV* fusion | <5% | Yes |
| | t(7;22)(p22;q12) | *EWS-ETV1* fusion | <5% | Yes |
| | t(17;22)(q12;q12) | *EWS-E1AF* fusion | <5% | Yes |
| | inv(22)(q12q12) | *EWS-ZSG* | <5% | Yes |
| Fibrosarcoma, infantile | t(12;15)(p13;q26) | *ETV6-NTRK3* fusion | >75% | Yes |
| | Trisomies 8, 11, 17, and 20 | | >75% | Yes |
| Gastrointestinal stromal tumor | Monosomies 14 and 22 | | >75% | Yes |
| | Deletion of 1p | | >25% | No |
| | | *KIT* mutation | >90% | Yes |
| Giant cell tumor | Telomeric associations | | >50% | ? |
| Hibernoma | 11q13 rearrangement | | >50% | Yes |
| Inflammatory myofibroblastic tumor | 2p23 rearrangement | *ALK* fusion genes | 50% | Yes |
| Leiomyoma | | | | |
| Uterine | t(12;14)(q15;q24) or deletion of 7q | *HMGIC* rearrangement | 40% | Yes |
| Extrauterine | Deletion of 1p | | ? | ? |
| Leiomyosarcoma | Deletion of 1p | | >50% | No |
| Lipoblastoma | 8q12 rearrangement or polysomy 8 | *PLAG1* oncogenes | >80% | Yes |
| Lipoma | | | | |
| Typical | 12q15 rearrangement | *HMGIC* rearrangement | 60% | Yes |
| Spindle cell or pleomorphic | Deletion of 13q or 16q | | >75% | Yes |

| | | | | |
|---|---|---|---|---|
| Aytpical (see well-differentiated liposarcoma) | | | | |
| Chondroid | t(11;16)(q13;p12–13) | | ? | Yes |
| Liposarcoma | | | | |
| Well differentiated | Ring form of chromosome 12 | | >75% | Yes |
| Myxoid/round cell | t(12;16)(q13;p11.2) | *TLS-CHOP* fusion | >75% | Yes |
| | t(12;22)(q13;q12) | *EWS-CHOP* fusion | <5% | Yes |
| Pleomorphic | Complex* | | 90% | No |
| Malignant fibrous histiocytoma | | | | |
| Myxoid | Ring form of chromosome 12 | | ? | ? |
| High grade | Complex* | | >90% | No |
| Myxofibrosarcoma | *See* Malignant fibrous histiocytoma | | | |
| Malignant peripheral nerve sheath tumor | *See* Schwannoma | | | |
| Mesothelioma | Deletion of 1p | *?BCL10* inactivation | >50% | Yes |
| | Deletion of 9p | *CDKN2A*, *CDKN2B*, and *CDKN2D* inactivation | >75% | Yes |
| | Deletion of 22q | *NF2* inactivation | >50% | Yes |
| | Deletions of 3p and 6q | | >50% | Yes |
| Neuroblastoma | | | | |
| Good prognosis | Hyperdiploid, no 1p deletion | | 40% | Yes |
| Poor prognosis | 1p deletion | | 40% | Yes |
| | Double minute chromosomes | *MYCN* amplification | >25% | Yes |
| Osteochondroma | Deletion of 8q | *EXT1* inactivation | >25% | ? |
| Osteosarcoma | | | | |
| Low grade | Ring chromosomes | | >50% | Yes |
| High grade | Complex* | *RB1* and *TP53* inactivation | >80% | ? |
| Pigmented villonodular synovitis | Trisomies 5 and 7 | | >25% | ? |
| Primitive neuroectodermal tumor | *See* Ewing's sarcoma | | | |
| Rhabdoid tumor | Deletion of 22q | *INI1* inactivation | >90% | Yes |
| Rhabdomyosarcoma | | | | |
| Alveolar | t(2;13)(q35;q14) | *PAX3-FKHR* fusion | >75% | Yes |
| | t(1;13)(p36;q14), double minutes | *PAX7-FKHR* fusion | 10–20% | Yes |
| Embryonal | Trisomies 2q, 8 and 20 | | >75% | Yes |
| | | Loss of heterozygosity at 11p15 | >75% | Yes |
| Schwannoma | | | | |
| Benign | Deletion of 22q | *NF2* inactivation | >80% | Yes |
| Malignant, low grade | None | | | |
| Malignant, high grade | Complex* | | >90% | No |
| Synovial sarcoma | | | | |
| Monophasic | t(X;18)(p11.2;q11.2) | *SYT-SSX1* or *SYT-SSX2* fusion | >90% | Yes |
| Biphasic | t(X;18)(p11.2;q11.2) | *SYT-SSX1* fusion | >90% | Yes |

*Consistent finding of extremely complex karyotypes containing multiple numerical and structural chromosomal aberrations.

| Histologic findings | Characteristic cytogenetic events | Molecular events | Frequency | Diagnostic utility? |
|---|---|---|---|---|
| Adenoid cystic carcinoma | 6q translocations and deletions | | >50% | Yes |
| Germ cell tumor | Isochromosome 12p | | >75% | Yes |
| Hepatoblastoma | Trisomies 2q and 20 | | >75% | Yes |
| Medulloblastoma | Isochromosome 17q | | >25% | Yes |
| Meningioma | Monosomy 22 | | 90% | Yes |
| | 1p deletion | | 25% | Yes |
| Midline lethal carcinoma | t(15;19)(q14;p13) | *BRD4-NUT* fusion | >75% | Yes |
| Oligodendroglioma | Deletion of 1p and 19q | | 50% | No |
| Pleomorphic adenoma (salivary gland) | 8q12 rearrangement | *PLAG1* fusion oncogenes | >50% | Yes |
| | 12q15 rearrangement | *HMGIC* oncogenes | <20% | Yes |
| Renal carcinoma | | | | |
| Clear cell | Deletion of 3p | | >90% | Yes |
| Papillary adult | Trisomies 3, 7, 16, 17, and 20 | | >90% | Yes |
| Papillarylike, young adults | Xp11 rearrangement | *TFE3* fusion | >50% | Yes |
| | 6p21 rearrangement | *TFEB* fusion | >50% | Yes |
| Oncocytoma | Monosomy 1 with loss of X or Y | | >25% | Yes |
| | 11q13 rearrangement | | >25% | Yes |
| Chromophobe | Monosomies 1, 2, 3, 6, 10, 13, 17, and 21 | | >75% | Yes |
| Thyroid carcinoma | | | | |
| Papillary | 10q11.2 rearrangement | *RET* fusion oncogenes | >30% | Yes |
| | 1q21 rearrangement | *NTRK1* fusion oncogenes | >10% | Yes |
| Follicular | t(2;3)(q13;p25) | *PAX8-PPARG* fusion | >40% | Yes |
| Mucoepidermoid carcinoma | t(11;19)(q21;p13) | *MECT1-MAML2* fusion | >50% | Yes |

# SOLID-TUMOR CYTOGENETICS

The factors determine the success of solid-tumor cytogenetics:

1. Unpredictable growth of the neoplastic cells in tissue culture.

2. Overgrowth of neoplastic cells by “reactive” non-neoplastic cells ( fibroblasts, normal epithelial cells, endothelial cells, or glial cells) - is the most common explanation for a normal diploid karyotype in solid-tumor cytogenetics.

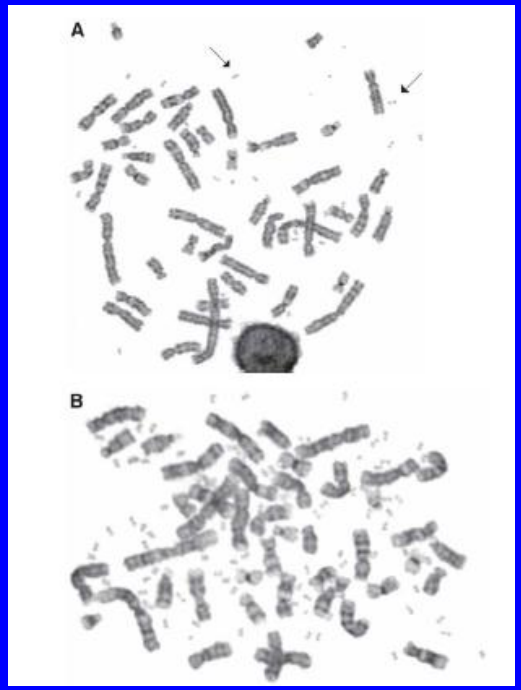
3. Destruction of tumor cultures by bacterial or fungal infection.

4. Failure of tumor cultures to grow because of nonviable tumor. Many solid tumors, particularly those that are highly malignant, are largely composed of nonviable regions, or regions with few neoplastic cells (extensively necrotic, hemorrhage or scarred tissue (fibrosis)). Therefore, it is crucial that the pathologist select a maximally viable tumor region for the solid-tumor cytogenetic analysis.

# CYTOGENETIC MECHANISMS IN SOLID TUMORS

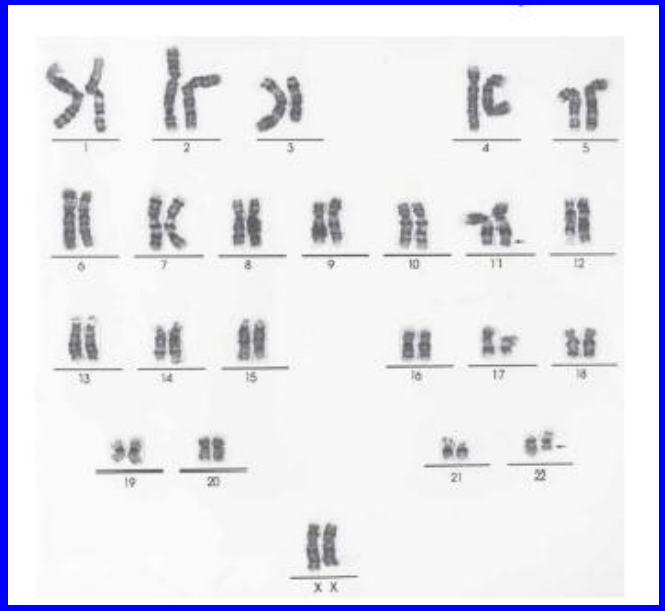
The cytogenetic aberrations in solid tumors vary from extremely simple, involving loss or rearrangement of a single chromosome, to highly complex. Complex abnormal karyotypes, which typically contain numerous clonal and nonclonal chromosomal aberrations, are most often found in highly malignant solid tumors. On the other hand, noncomplex karyotypes can be found in either benign or malignant tumors.

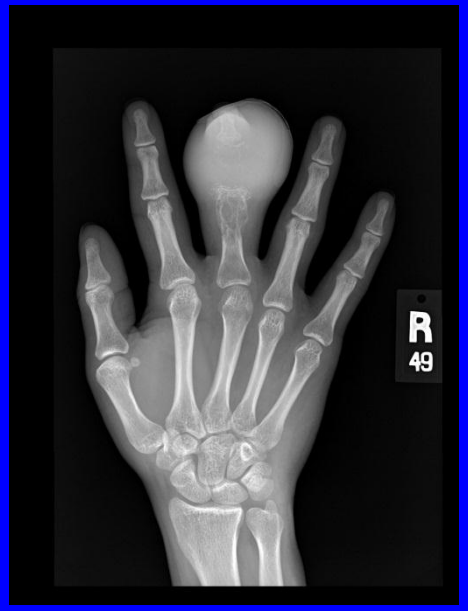
The chromosome aberrations in solid tumors result in translocation, deletion, or amplification of target genes. Translocations are particularly frequent in sarcomas, where they usually create fusions of genes at the breakpoints of the participant chromosomes. Deletions are frequent in carcinomas, where they likely result in loss of tumor suppressor genes. Amplifications, which are manifest as intrachromosomal homogeneously staining regions or as extrachromosomal double minutes are seen occasionally in solid tumors of all types and can be of both prognostic and therapeutic relevance.

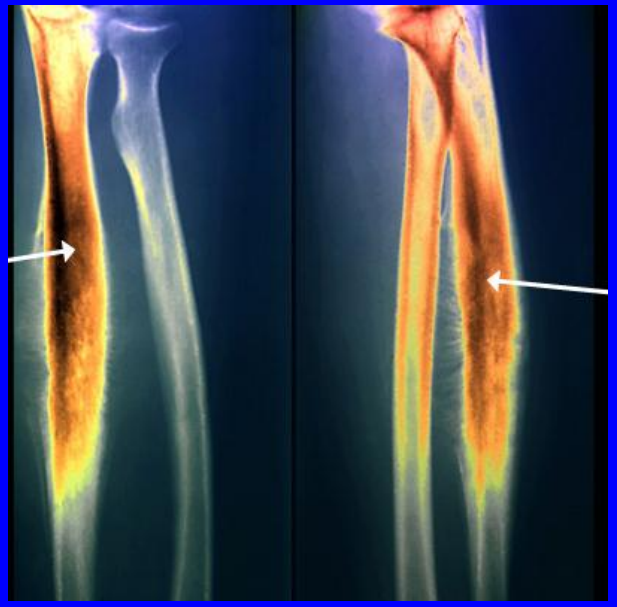


# MESENCYMAL TUMORS (SOFT TISSUE AND BONE TUMORS): Ewing's Sarcoma

Ewing's sarcomas are highly aggressive bone and soft tissue tumors, in which the neoplastic cells are generally of the small round cell type. Most Ewing's sarcomas contain chromosome translocations involving the Ewing's sarcoma gene (EWS), which is located on the long arm of chromosome 22. These translocations involve a number of partner genes; the most common rearrangement is t(11;22)(q24;q12), which results in oncogenic fusion of the FLI1 gene on chromosome 11 with the EWS gene.





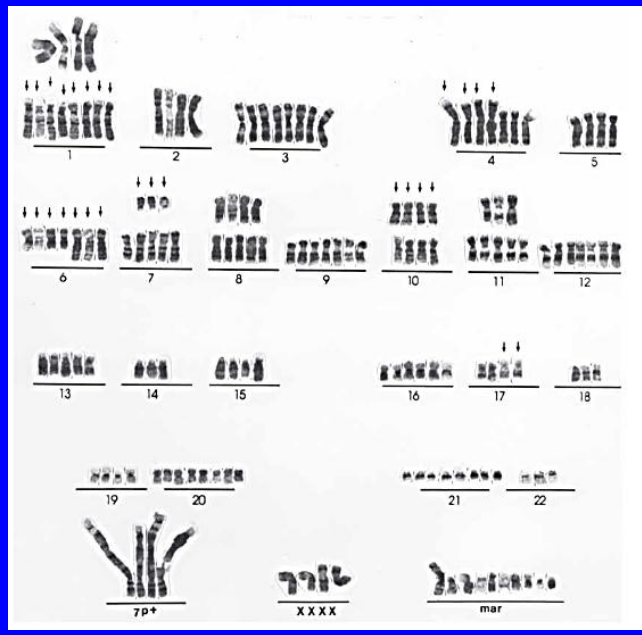



# MESENCYMAL TUMORS (SOFT TISSUE AND BONE TUMORS): Smooth Muscle Tumors

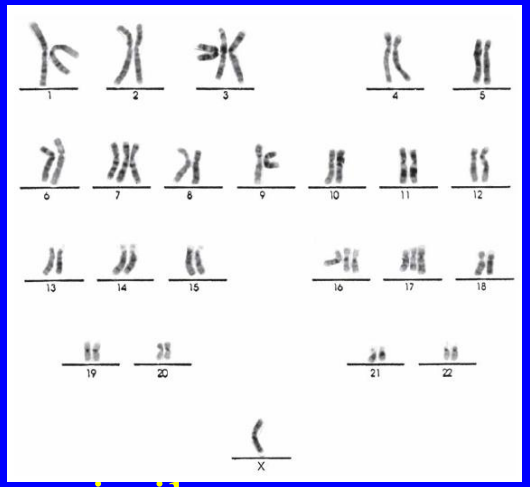
Malignant smooth muscle tumors (i.e., leiomyosarcomas) generally have complex karyotypes, but the most consistent finding has been deletion of the short arm of chromosome 1. The cytogenetic complexity in leiomyosarcomas can be striking even in low-grade specimens.

Benign smooth muscle tumors (leiomyomas), particularly those of uterine origin, contain various translocations and deletions, but generally in the context of a simple karyotype. Approximately 50% of benign leiomyomas lack evident cytogenetic aberrations.

Deletions of the long arm of chromosome 7 are found in 15–25% of uterine leiomyomas, whereas trisomy 12 and rearrangements of the short arm of chromosome 6 are each found in approximately 10–15% of cases. However, the most distinctive cytogenetic abnormality in leiomyoma is a translocation involving chromosomes 12 and 14 that is found in approximately 20% of uterine cases.



# EPITHELIAL TUMORS:
# Papillary Renal Carcinomas



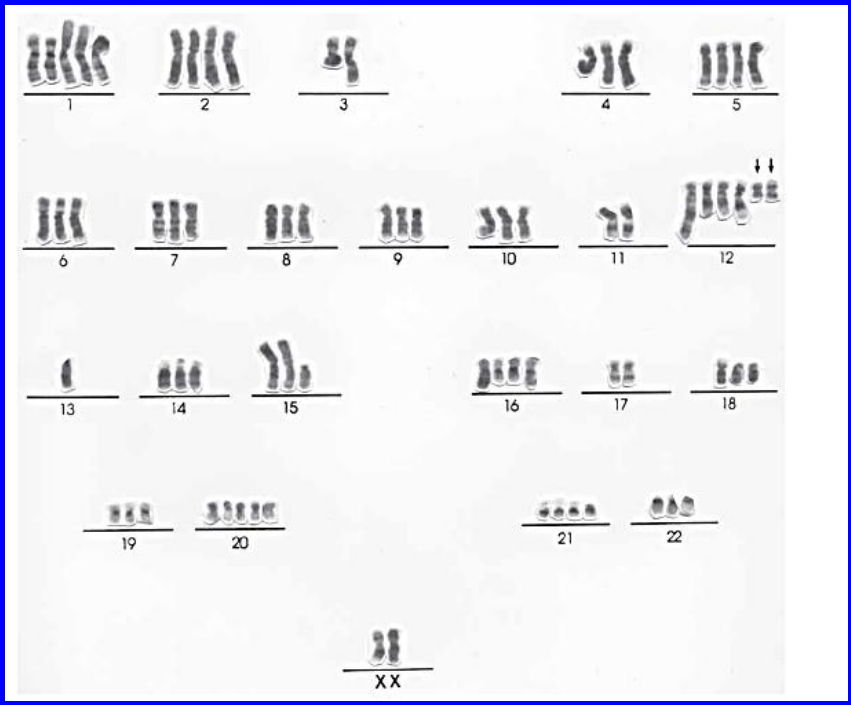
Approximately 10% of all renal carcinomas are papillary, and the cytogenetic profiles for papillary renal cell carcinomas are distinctive. It has been proposed that papillary renal neoplasms smaller than 3 cm be classified as benign adenomas, whereas those larger than 3 cm should be classified as carcinomas.

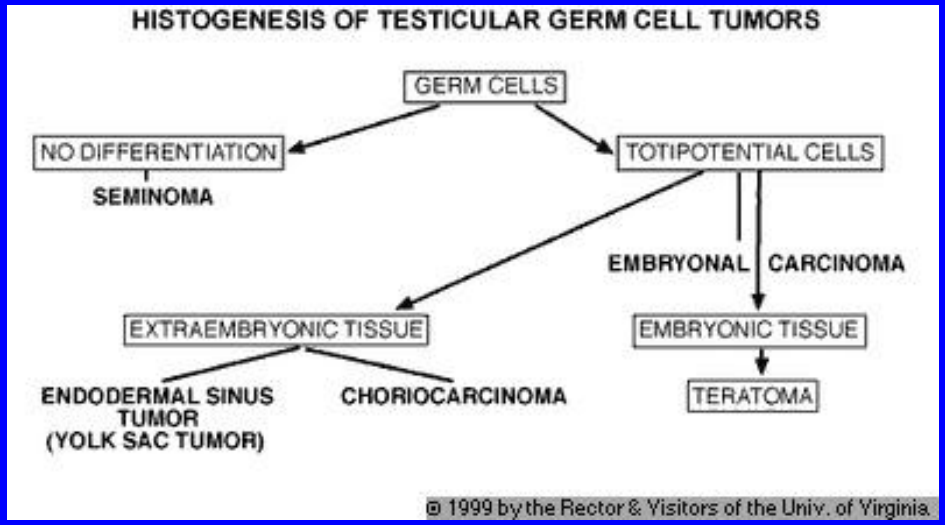
Renal adenomas and papillary carcinomas contain a similar core group of chromosome aberrations (–Y,+7, +17).

The most frequent cytogenetic aberrations in papillary renal cell carcinomas include trisomies of chromosomes 7, 16, and 17, and loss of the Y chromosome; each of these aberrations is found in at least 50% of papillary renal cell carcinomas. Additional nonrandom chromosome aberrations, which are found in 10–50% of papillary renal cell carcinomas, include trisomies 3, 8, 12, and 20. In contrast, clear cell/granular carcinomas rarely have trisomies 16 or 17, but virtually always have a cytogenetic deletion of 3p14–21, which is found in fewer than 10% of papillary renal cell carcinomas.

# GERM CELL TUMORS

Many germ cell tumors contain a characteristic cytogenetic marker, isochromosome 12p, which is often found in the context of a moderately complex karyotype, with clonal polysomies and rearrangements of various other chromosomes. The isochromosome 12p is uncommon, albeit not unprecedented in carcinomas and sarcomas. Therefore, demonstration of isochromosome 12p, particularly in any poorly differentiated cancer, should provoke strong suspicion of a germ cell origin, but should not be taken as de facto evidence of such origin.



***Thank you for attention!***