

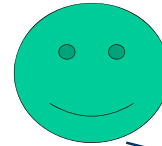
Cytogenetic Abnormalities in Hematologic Disorders

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Oncogenesis



Increased Growth and Survival



Down-regulated Death and Apoptosis

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Objectives

- Understand the genetic basis of neoplastic diseases
- Basic principles of chromosome analysis
- Different types of chromosome abnormalities
- Means to identify the abnormalities

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Oncogenes and Tumor Suppressor Genes

Oncogenes

- Normally function to promote cell growth and division
- Mutation/overexpression causes uncontrolled growth

Tumor Suppressor Genes

- Normally function to suppress cell growth and division
- Inactivation causes uncontrolled growth

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Normal Growth and Cell Cycle



Growth and Survival



Death and Apoptosis



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Activation of Oncogenes

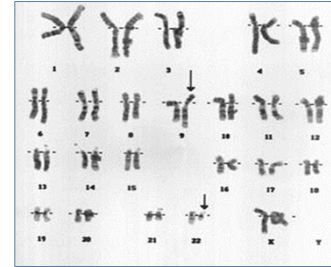
- Point Mutations
- Chromosome Translocations
- Gene Amplification

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Methods to Identify Genetic basis of Diseases

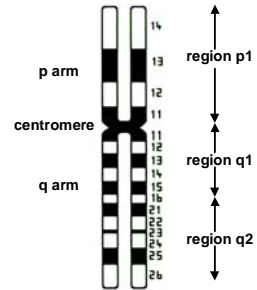
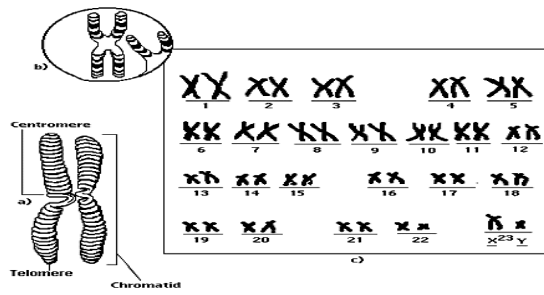
- Chromosome analysis (Karyotyping)
- FISH
- PCR
- mRNA and micro RNA
- Proteomics

Philadelphia Chromosome of CML



The abnormality seen by Nowell & Hungerford on chromosome 22. Now known as the Philadelphia Chromosome.

Human Chromosomes



Normal metaphase vs. Normal male karyogram

Normal metaphase



Normal male karyogram



46, XY

Nomenclature

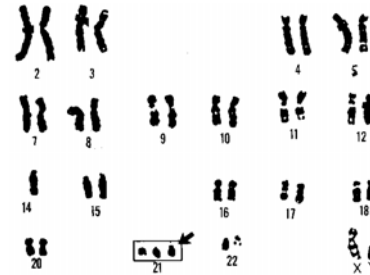
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Chromosome Disorders

- Conditions associated with visible changes in chromosomes
 - Limited to fairly large gains, losses or rearrangements of chromosomal material

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Trisomy 21



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Clinical Cytogenetics

- **Acquired Abnormalities**
 - Leukemia and lymphoma
- **Constitutional Abnormalities**
 - Prenatal diagnosis
 - Newborns/children with multiple congenital abnormalities
 - Adults with infertility

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Consequences of Chromosome Abnormalities in Cancer

- **Translocations**
 - Fusion proteins
 - Overexpression of normal proteins
- **Deletions**
 - Loss of tumor suppressor genes
- **Amplifications of genes**
 - Oncogene overexpression

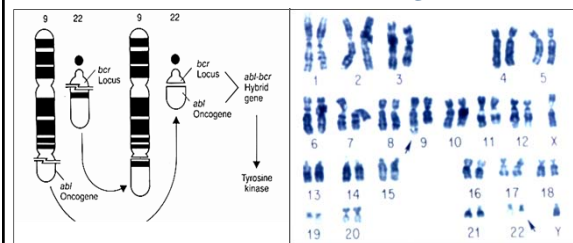
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Types of chromosome abnormalities

- **Numeric abnormalities**
 - Diploid, haploid, aneuploid, tetraploid, monosomy, trisomy
- **Structural abnormalities**
 - Translocations, deletions, duplications, inversions, rings

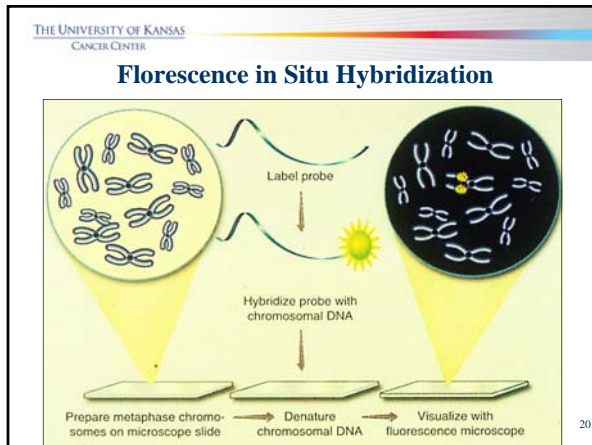
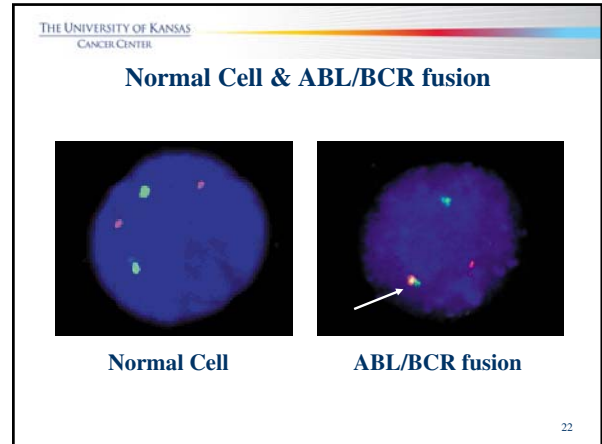
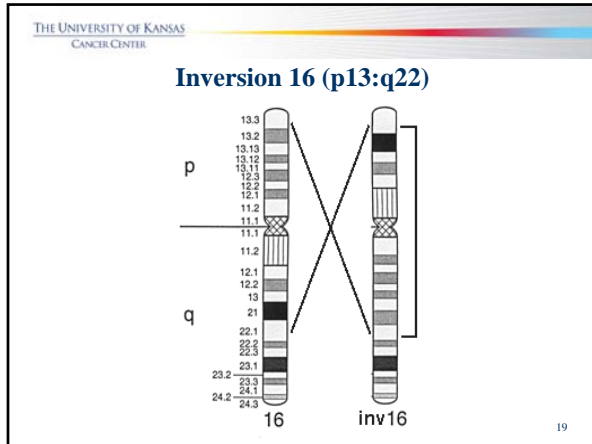
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Mechanisms by which chromosome translocations active oncogenes

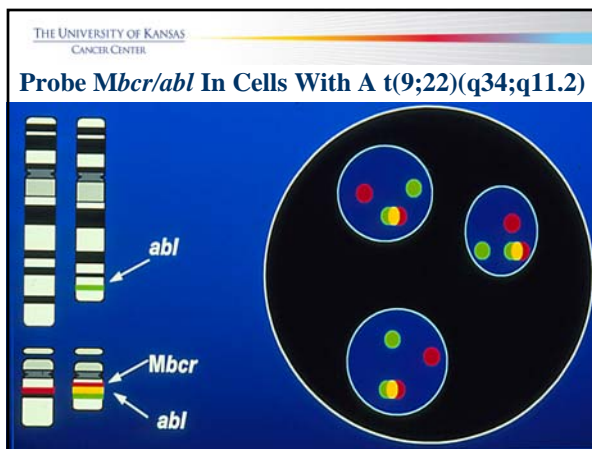


Fusion protein- *bcr/abl* in chronic myelogenous leukemia increased tyrosine kinase activity

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- ### Let us Read a Report!
- 70 year old male admitted with acute leukemia add 16 (p2.1); del 3q13; t(8:14)(q24;q32); der 16p32/44-46 XY; FISH was positive for t(8:14)(c-myc:IgH)(q24;q32)
 - Flow cytometry was suggestive of pre-B ALL
 - Treated with Hyper CVAD
 - After 2 cycles: 46, XY
 - After 4th cycle relapsed with: add 16 (p2.1); del 3q13; -7; t(8:14)(q24;q32); der 16p32/44-46 XY
 - Clonal evolution and planning for cord blood transplantation
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- ### What we learned!
- Understood the genetic basis of neoplastic diseases
 - Basic principles of chromosome analysis
 - Different types of chromosome abnormalities
 - Means to identify the abnormalities by Karyotyping and FISH
 - **How to read a report**
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