Cytogenetic Abnormalities in Hematologic Disorders

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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

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

Normal Growth and Cell Cycle

Activation of Oncogenes

• Point Mutations
• Chromosome Translocations
• Gene Amplification
Methods to Identify Genetic basis of Diseases

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

Human Chromosomes

Normal metaphase vs. Normal male karyogram

Normal metaphase

Normal male karyogram

Nomenclature

22q11.2
Chromosome Disorders

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

Clinical Cytogenetics

- Acquired Abnormalities
  - Leukemia and lymphoma

- Constitutional Abnormalities
  - Prenatal diagnosis
  - Newborns/children with multiple congenital abnormalities
  - Adults with infertility

Types of chromosome abnormalities

- Numeric abnormalities
  - Diploid, haploid, aneuploid, tetraploid, monosomy, trisomy

- Structural abnormalities
  - Translocations, deletions, duplications, inversions, rings

Consequences of Chromosome Abnormalities in Cancer

- Translocations
  - Fusion proteins
  - Overexpression of normal proteins

- Deletions
  - Loss of tumor suppressor genes

- Amplifications of genes
  - Oncogene overexpression

Mechanisms by which chromosome translocations active oncogenes

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

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