Cytogenetics for The Internist

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INTRODUCTION

Chromosomes are distinct dense bodies found in the nucleus of cells, composed of protein and DNA, containing genetic information in the form of linear sequences of bases (A,T,C,G). The DNA in an individual chromosome is one, long molecule which is highly coiled and condensed (figure 1).The total number of bases in all the chromosomes of a human cell is approximately six billion and individual chromosomes range from 50 to 250 million bases. The DNA sequence for a single trait is called a gene. Each chromosome contains a few thousand genes, which range in size from a few thousand bases up to 2 million bases.

During most of the cell cycle, interphase, the chromosomes are somewhat less condensed and are not visible as individual objects under the light microscope. However during cell division, mitosis, the chromosomes become highly condensed and are then visible as dark distinct bodies within the nuclei of cells. The chromosomes are most easily seen and identified at the metaphase stage of cell division and most of the chromosome images are pictures of metaphase chromomosomes.

The number of chromosomes in human cells is 46 with 22 autosomal pairs (one of each type contributed by the mother and one of each type from the father) and 2 sex chromosomes-2 X chromosomes for females (one from father and one from mother) or an X and a Y chromosome for males (the X from the mother and the Y from the father).

Some diseases, notably malignancies or cancer, are the results of genetic changes which often are seen-in some cases, first detected as–chromosomal changes. The German pathologist David von Hamsemann in 1890 was the first to be impressed by the frequent occurrence of nuclear and mitotic irregularities and suggested that these phenomena were important to the origin and development of malignancy. A quarter of a century later, Theodor Boveri presented his systematic mutation theory, in which he surmised that chromosomal abnormalities were the cellular changes causing the transition from normal to malignant proliferation. Thus was born the study of chromosomes and their abnormalities, known as cytogenetics, and in the four decades since the chromosome number of man was correctly determined to be 46 by Tjio and Levan, it has developed into one of the most rapidly growing areas in human genetics.

DEVELOPMENT

A very important finding in cancer cytogenetics has been the detection of a small "marker" chromosome by Nowell and Hungerford ikn 1960, subsequently named the "Philadelphia Chromosome", and found to be distinctly related to chronic myelogenous leukemia (CML). It was a spectacular finding but was not followed by other reports, and interest in cytogenetics waned until the introduction of the chromosome banding technique by Casperssopn et al in 1970, which completely revolutoionized cytogenetic analysis, as each chromosome could be identified on the basis of its unique banding patter.

The characteristic banding of chromosomes is obtained by staining with various dyes (Giemsa in the author's laboratory at the University of Indonesia Faculty of Medicine). The banding of chromosomes by using dyes was discovered in the late 1960's and before that cytogeneticists depended on chromosome length and position of a constriction to identify the individual chromosomes. The band width and the order of bands is characteristic of a particular chromosome-a trained cytogeneticist can identify each chromosome (1,2,3,...22, X and Y) by observing its banding pattern under the microscope. Whereas formerly identification was restricted to chromosome groups (A, B, C, D,....), all descriptions

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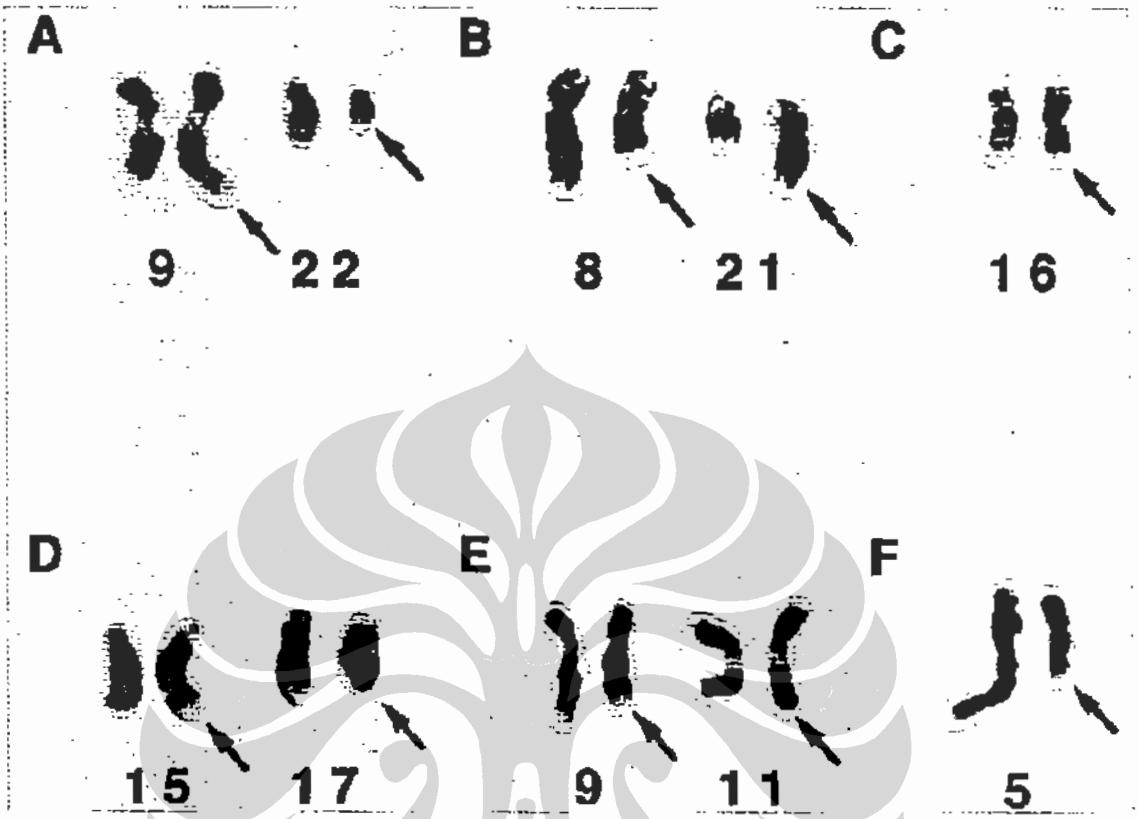

Figure 5. Various translocations, each having diagnostic and / or prognostic significance. Note: the translocation of chromosome 9 and 22, previously known as the smaller chromosome 22 was known as the Philadelphia Chromosome and the first clinically significant chromosome aberration reported. Translocations between chromomsomes 8 and 21, 15 and 17 and the inversion of chromosome 16 (B.C and D) herald a good prognosis and better response to chemotherapy whereas deletion of chromosome 5 (F) carries a poor prognosis.

somes 5, 7, and trisomy 8, changes connected with secondary or treatment-related leukemias, as cytogenetic abnormalities having poor prognosis (figure 2)

In the diagnosis of acute leukemia, the morphological basis of diagnosis (only) has been replaced with the "MIC" or Morphology–Immunphenotyping–Cytogenetics, currently employing the three different techniques and interpretation, a *conditio sine qua non* or prerequisite for a scientifically sound clinical judgement. The weaknesses of one diagnostic modality will be negated by the strenght of the other. And for the internist, who has to make decisions based on a holistic approach utilizing all the data available, cytogenetic analysis will be a valuable and necessary tool.

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