Chromosomes in Biology and Medicine

New Chromosomal Syndromes

Edited by

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Molecular Structure of Human Chromosomes, 1977

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Preface

In the last few years, technical advances have taken place that have revolutionized the field of medical cytogenetics. Amniocentesis is now a common and safe procedure, allowing early study of the fetus. Banding techniques have provided easy identification of each chromosome and the means for recognition of chromosome abnormalities ranging from minute defects to complex rearrangements. Thousands of case reports have appeared in the recent literature describing partial trisomies and partial deletions for every chromosome. Of clinical importance is the fact that close to one percent of newborns are now found to have a chromosome defect, and, in many instances, the affected individuals have a parent with a balanced chromosome translocation, allowing possible prevention of recurrence of the disease with counseling and prenatal diagnosis.

This volume brings together, for the first time, all the clinically relevant information related to birth defects and chromosomes that has accumulated during the last six years. Emphasis is placed on the detailed description of approximately thirty new chromosomal disorders for which there are sufficient data to substantiate their clinical delineation. In addition, the reader will find extensive review of the classic chromosome disorders, the new chromosome techniques, and phenotype–chromosome relationships.

For geneticists, human biologists, cytologists, and members of the medical profession involved in the study of birth defects–pediatricians, obstetricians, and pathologists alike–this book should serve as a valuable, authoritative guide.

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Jorge J. Yunis

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New Chromosome Techniques and Their Medical Applications

OTTO SANCHEZ and JORGE J. YUNIS

I. INTRODUCTION

In 1956, a major turning point occurred in the field of human cytogenetics when Tjio and Levan reported the correct number of chromosomes in man. In the following years, the introduction of relatively simple techniques for lymphocyte cultures and chromosome preparations (Hungerford *et al.*, 1959; Moorhead *et al.*, 1960) allowed human cytogenetics to become a discipline on its own. Several well-

defined autosomal syndromes (Lejeune, 1959; Patau *et al.*, 1960; Edwards *et al.*, 1960; Lejeune *et al.*, 1963) were then described, sex chromosome anomalies (Turner and Klinefelter syndromes) were confirmed by karyotype analysis, and the association between the Ph^1 chromosome and chronic myelogenous leukemia was firmly established (Nowell and Hungerford, 1960). Autoradiographic techniques served later to identify the X chromosome as well as the autosomes more frequently involved in autosomal anomalies (Yunis, 1965). By the mid-1960's, however, the original impetus seemed to have been lost and the field reached a plateau of little new information. Most of the difficulties resided in the fact that cytogeneticists were unable to identify reliably most of the human chromosomes and, although many cases bearing abnormal chromosomes or chromosome segments were known, a correlation between clinical signs and chromosomal abnormalities was fraught with difficulties.

In 1968, Caspersson *et al.* reported a distinctive fluorescence pattern in plant chromosomes after quinacrine mustard staining. The importance of these findings was not immediately realized until Caspersson *et al.* (1970a) applied the same technique to human chromosomes and demonstrated a specific banding pattern for each chromosome pair. The pioneer work of Caspersson's group proved to be the beginning of an explosive development in that area. Since that time, numerous other techniques have been described that allow the visualization of differentially stained regions in the chromosomes. The application of these techniques to human chromosomes has dramatically changed the field of human cytogenetics. New chromosomal defects involving almost every chromosome of the human complement have been described (Lewandowski and Yunis, 1975), classical syndromes have been subdivided according to the chromosomal segment involved (Chapter 9), phenotypic mapping of chromosomes now seems possible (Chapter 12), chromosomal polymorphisms have been shown to be of universal occurrence (see Section IV, B), and previously unsuspected chromosomal rearrangements have been demonstrated (Gray *et al.*, 1972; Pasquali, 1973; Koulischer and Lambrotto, 1974).

It is now becoming apparent that there are chromosomal segments that in the trisomic state might not be as harmful as other segments, and that small chromosomal abnormalities may be compatible with normal or slightly affected phenotypes (Friedrich and Nielsen, 1974; Lewandowski *et al.*, 1976; see also Chapter 8).

The impact produced by the banding techniques has not been limited to clinical cytogenetics; these techniques have made important contributions to other scientific areas as well. Human gene mapping, for example, is a rapidly developing field which owes many of its recent advances to the aid given by the banding methods. The study of the molecular organization of chromosomes is

another area of research that has been influenced by these advances (Yunis, 1977a; Yunis and Chandler, 1977a). In the following sections, a general description of the banding techniques and chromosomal bands will be given, as well as introductory concepts on chromosome identification and current cytogenetics terminology. Some of the clinical applications are also reviewed.

II. THE PARIS CONFERENCE

After the first banding techniques were described, a need became evident for international agreement on a nomenclature system to identify the chromosomal bands. In 1971, an international conference was held in Paris for this specific purpose. The recommendations made by this conference (Paris Conference, 1971) have been widely accepted and are amply used in the current cytogenetic literature. Some of the recommendations of the Paris Conference are outlined below, and examples are given to aid in understanding the terminology.

The nomenclature symbols already suggested by the Chicago Conference (1966) were retained with minor modifications and some additional symbols were added (Table I). It was agreed to use the term "Q-bands" to refer to those bands obtained by the quinacrine mustard banding technique. "C-bands" was the name applied to bands shown by the techniques that stain constitutive heterochromatin. "G-bands" was given to those bands obtained with Giemsa stain, with the exception of the "R-bands" which designate those bands resulting from a particular technique and which are, in general, the opposite of the Q- and G-bands.

Banded chromosomes were considered to consist of a continuous series of light and dark bands, so that, by definition, there are no interbands. Thus, a "band" was defined as a part of a chromosome which is clearly distinguishable from its adjacent segments by appearing darker or lighter with the Q-, G-, C- or R-staining methods.

Fluorescent positive bands elicited by the Q-banding technique generally correspond to those darkly stained with the G-banding methods, while the pale fluorescent or negative Q-bands are, in general, the same chromosomal areas that remain lightly stained with the G-banding techniques. The opposite pattern is followed by the R-bands, where those areas that appear positive (fluorescent or dark) with Q- and G-bands are shown as very lightly stained areas and vice-versa. Exceptions to this rule are represented by the heterochromatic regions of chromosomes 1, 9, and 16, which will be discussed below. It should be noted that, in reality, there are no "negative" regions since the whole chromosome is stained; rather, the intensity varies from almost no fluorescence (or very light

TABLE I
Nomenclature Symbols

Chicago Conference	
A–G	the chromosome groups
1–22	the autosome numbers
X,Y	the sex chromosomes
diagonal (/)	separates cell lines in describing mosaicism
?	questionable identification of chromosome or chromosome structure
*	chromosome explained in text or footnote
ace	acentric
cen	centromere
dic	dicentric
end	endoreduplication
h	secondary constriction or negatively staining region
i	isochromosome
inv	inversion
mar	marker chromosome
mat	maternal origin
p	short arm of chromosome
pat	paternal origin
q	long arm of chromosome
r	ring chromosome
s	satellite
t	translocation
repeated symbols	duplication of chromosome structure

continued

Giemsa staining) to very brilliant fluorescence (or dark Giemsa staining), with other areas showing intermediate degrees of fluorescence or staining (pale, medium, or intense).

The specific banding patterns obtained in each chromosome pair by the use of the Q-banding technique were used to construct an idiogram of the human banded karyotype for the purposes of chromosome identification (Fig. 1). Certain "constant and distinct morphological features that are important aids in identifying a chromosome" were selected as "landmarks." The centromeres, telomeres, and some well-defined bands were included in this definition. The chromosomal arms were divided into "regions"; a region was defined as "any area of a chromosome lying between two adjacent landmarks." A chromosome arm lacking any prominent landmark was considered to consist of only one region. In each chromosome, the centromere served as a reference point for the numbering of regions and bands. The chromosome arms were first divided into regions according to the landmarks selected by the Paris Conference. In each arm, the region closest to the centromere was identified as Number 1, and other regions,

TABLE I (*continued*)

Paris Conference

A. Recommended changes in Chicago Conference nomenclature

\+ 1. The + and – signs should be placed *before* the appropriate symbol where they mean – additional or missing whole chromosomes. They should be placed *after* a symbol where an increase or decrease in length is meant. Increases or decreases in the length of secondary constrictions, or negatively staining regions, should be distinguished from increases or decreases in length owing to other structural alterations by placing the symbol h between the symbol for the arm and the + or – sign (e.g., 16qh+).

2. All symbols for rearrangements are to be placed before the designation of the chromosome(s) involved in the rearrangement, and the rearranged chromosome(s) always should be placed in parentheses, e.g., r(18), i(Xq), dic(Y).

B. Recommended additional nomenclature symbols

del	deletion
der	derivative chromosome
dup	duplication
ins	insertion
inv ins	inverted insertion
rcp	reciprocal translocation[a]
rec	recombinant chromosome
rob	Robertsonian translocation[a] ("centric fusion")
tan	tandem translocation[a]
ter	terminal or end ("pter" for end of short arm; "qter" for end of long arm)
:	break (no reunion, as in terminal deletion)
::	break and join
→	from – to

[a]Optional, where greater precision is desired than that provided by the use of t as recommended by the Chicago Conference.

if present, numbered consecutively toward the telomeric ends; the bands present within each region were, in turn, numbered following the same rules applied to the regions. A description of the specific banding patterns of each chromosome with emphasis on prominent landmarks and other characteristics useful for chromosome identification can be found in Rowley (1975).

Using the Paris Conference suggestions, any particular band or segment of a chromosome can be easily identified, and only four items are required: chromosome number, an arm symbol (p = short arm; q = long arm), the region and band numbers. No spacing or punctuation is used and the order of the items may not be changed. For example, 6p23 indicates band number 3 of region 2 in the short arm of chromosome 6 (see Fig. 2A). Provisions were also made for the subdivi-

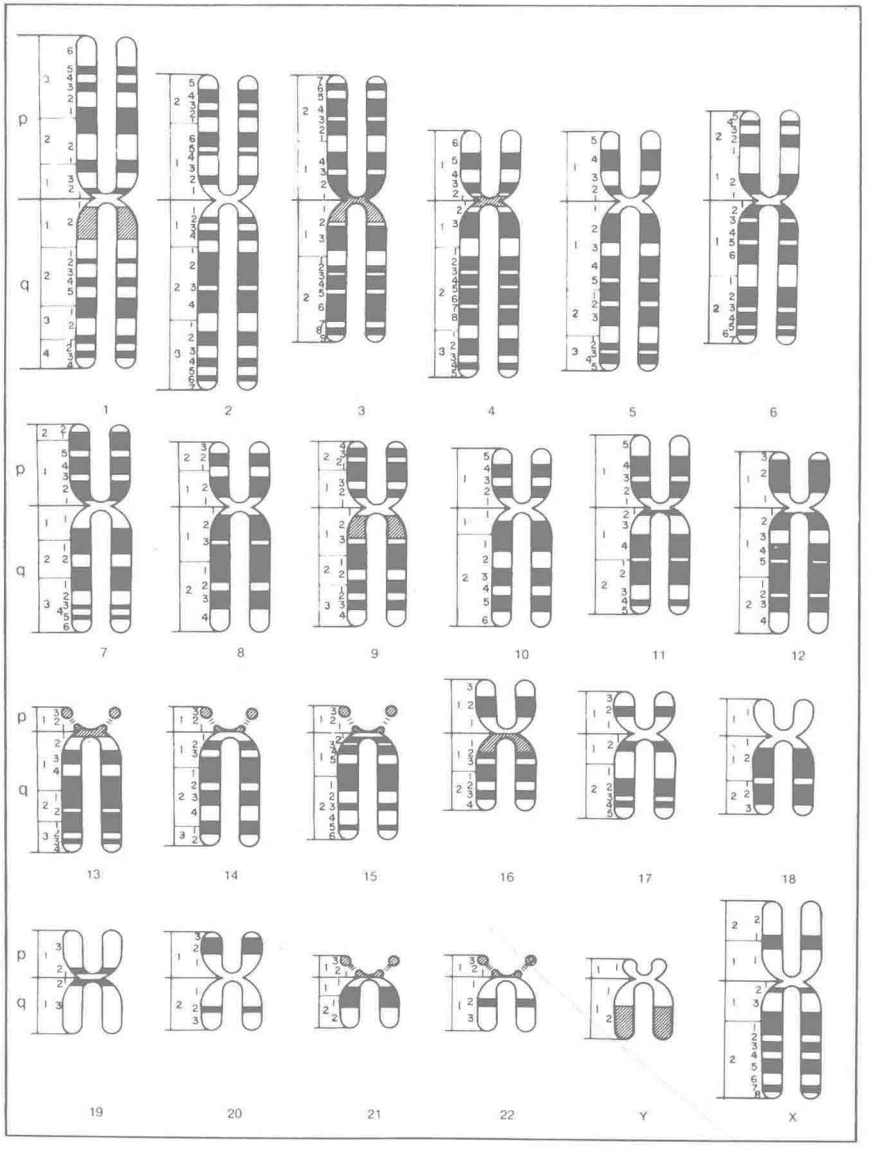

Fig. 1. Diagrammatic representation of metaphase chromosome bands as observed with the Q- and G-staining methods; centromere representative of Q-banding method only. Reproduced from the report of the Paris Conference (1971).