Genetics and Birth Defects in Clinical Practice

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Preface

During the 1950s genetic syndromes were matters of curiosity more than of science. Few physicians at that time were interested in syndromology, and our own mentor, Dr. Sydney S. Gellis, was one of the few pediatricians who lectured on this subject. In the 1960s many malformation syndromes were noted to be associated with a chromosomal or biochemical abnormality. Syndromology was becoming "respectable." Another milestone was the legendary Baltimore meetings chaired by Dr. Victor McKusick (in retrospect, and as time dims our memories, these meetings, like a seasoned wine, appear even more impressive with each passing year). As we continue to learn more about genetics and biochemical defects, syndromology is becoming more and more a part of the clinician's daily practice and hence the need for more clinical information concerning syndromes.

This book is divided into clinical and nonclinical parts. The first three chapters in Part I deal with basic issues: genes, chromosomes, and inheritance patterns. Hopefully it is enough to "whet the appetite" but not too limited to confuse the reader. With this background information the reader can then better understand the chapters on genetic counseling and prenatal diagnosis. The clinical evaluation chapter should be read prior to the descriptions of syndromes in Part II, because this chapter contains tables listing the differential diagnoses of various clinical manifestations and the clinical evaluation of patients with skeletal dysplasias. Part II consists of three sections: genetic and birth defect syndromes, skeletal dysplasias, and chromosomal abnormalities. Numerous syndromes are presented, and most of the more common ones are discussed. Some of the less common ones are also included because they are of significant interest or are one of the author's favorite syndromes. Some nongenetic syndromes are also included mainly because they need to be considered in the differential diagnosis. Bibliographies are provided so the reader can obtain more information if necessary. Various clinical measurements are described in the Appendix.

This book was written mainly for the practicing clinician, clinician in training, and student. Emphasis is placed on diagnosis, because without the correct diagnosis it is difficult to provide proper genetic counseling.

This book was not intended to be a treatise, but to serve as a guide to syndrome and birth defect diagnosis. It is a starting point. If it serves this function, we will consider it successful.

Special thanks to Lin Richter Paterson for her continued interest in the book, her encouragement and patience, and her friendship. Thanks also to Katherine Arnoldi, who always asked the right questions, thus making the text more readable.

M.F.
H.P.

Contents

I. Basic Genetics and Clinical Evaluation

1. The Gene

Genetic material consists of strands of deoxyribonucleic acid (DNA). The work of Watson and Crick showed that this material consists of a double-stranded helix as in a rope ladder. The ropes are made up of alternating deoxyribose and phosphate molecules, and the rungs consist of pairs of nucleotide bases; the ropes are twisted into a double helix. The nucleotides are guanine (G), cystosine (C), adenine (A), and thymidine (T). The physiochemical restrictions are such that G on one strand can pair only with C on the other, and A can pair only with T. Thus, the base sequence on one strand bears a complementary relationship to that of the other. When the DNA replicates, the two strands separate, and each lays down a new complementary strand, so that two new double helixes are formed, identical in base sequence with the original. The DNA in higher organisms is also associated with proteins, particularly histones, to form the microscopically visible chromosomes.

It is now well established that genes act by controlling the amino acid sequences of polypeptides and thereby the structures and properties of proteins. For each polypeptide synthesized, there is a corresponding region of a chromosome in which the sequence of base pairs in the DNA determines the amino acid sequence of the gene for the polypeptide. A mutant gene results in an altered amino acid sequence, which may alter the structure of the polypeptide and hence its properties. This leads to a genetically determined defect in the corresponding protein, be it an enzyme, as in the inborn errors of metabolism, or other proteins, as in the abnormal hemoglobins.

The genetic code is contained in the DNA in the chromosomes of the cell nucleus. Polypeptide synthesis takes place in the cytoplasm, in association with the cytoplasmic organelles called ribosomes. The link between DNA and polypeptides is RNA.

Ribonucleic acid (RNA) is a single-stranded molecule, very similar to one strand of the double-stranded molecule of DNA. All types of RNA are synthesized on a DNA template by direct transcription of the DNA code into a complementary RNA code. Transcription depends on RNA polymerase, a completed molecule, part of which recognizes the specific DNA triplet that signals the start of a gene. The polymerase "reads" the DNA gene, meanwhile forming a complementary molecule of RNA. When the polymerase reaches a terminator codon, the reading stops, and the completed RNA molecule is released.

Three kinds of RNA take part in the synthesis of protein: messenger, transfer, and ribosomal RNA.

Messenger RNA (mRNA) is formed in the nucleus on a template composed of one of the two strands of the DNA double helix and is structurally complementary to this strand. It passes from the nucleus to the cytoplasm, where it is found in association with ribosomes. The mRNA code, transcribed from the DNA of the chromosomes, prescribes the sequence in which amino acids are incorporated into a polypeptide.

Transfer RNA (tRNA) has a molecule much smaller than that of mRNA. Its function is to transfer amino acids from the cytoplasm to their specific places along the mRNA template. These amino acids must first be activated by special amino acid–activating enzymes, one for each amino acid. An activator enzyme recognizes a special site on the amino acid molecule and also a special recognition site on the tRNA molecule. At another site on the tRNA molecule is an anticodon, which recognizes a specific codon on the mRNA chain. Since several codons may code for one amino acid, one amino acid may be carried by several different tRNA molecules. It is not yet clear whether alternative codons are equally efficient and whether the alternative tRNA molecules are available in adequate quantities. The amino acid–transfer RNA (AA-tRNA) unit is placed in the appropriate position on the linear mRNA molecule by the matching of codon and anticodon.

Ribosomes consist of proteins and a nonspecific RNA (rRNA) in about equal proportions. The role of the ribosome is to adhere to a "sticky spot" on the mRNA molecule and then proceed along the mRNA, reading the code and bringing AA-tRNA units into line at the proper codons. Peptide bonds are then formed between the amino acids by an enzyme of the ribosome. Once the peptide bond is formed, the polypeptide chain begins to pull away from the ribosome.

FORMATION OF A POLYPEPTIDE CHAIN

The steps that lead to the formation of a polypeptide chain are as follows:

1. The two strands of DNA in the double helix dissociate in the area of the gene to be transcribed. Dissociation of the DNA strands appears to require no specific enzyme. Only one of the two DNA strands acts as a template for RNA synthesis.
2. A molecule of mRNA forms on the DNA template.
3. The mRNA moves into the cytoplasm.
4. In the cytoplasm, specific enzymes activate amino acid molecules and bring them into association with tRNA to form AA-tRNA complexes. Each enzyme activates only one kind of amino acid and attaches it to a specific tRNA that has a specific position ("anticodon") that is complementary to the appropriate codon on mRNA.
5. Ribosomes that are part protein and part nonspecific RNA adhere to specific "sticky points" on the mRNA molecule and move along the molecule. Under this influence, AA-tRNA complexes are lined up in the correct order along the mRNA chain, beginning at an adenine-uridine-guanine codon.

6. An enzyme in the ribosome causes the formation of peptide bonds between the amino acids of successive AA-tRNA complexes.
7. When the peptide bond has formed, the AA-tRNA complex breaks up, and the tRNA is free to unite with another activated AA.
8. As it is formed, the molecule of polypeptide swings away from the mRNA strand. In about 10 seconds, the ribosome reaches a terminator codon at the end of the gene and becomes available to form another polypeptide.

REGULATION OF GENE ACTIVITY

Not all genes are active in all cells at the same time, and the genes that are active may be synthesizing their respective proteins in varying amounts.

The understanding of how some genes are suppressed and others activated is the result of work done in bacterial genetics and with the formulation of the operon concept by Jacob and Monod. The *operon* is a group of genes arranged in linear order that produces a series of enzymes concerned with the same biosynthetic pathway. The first gene in the series contains the *operator,* which *initiates* the activity of the whole group. The operator can be activated or suppressed by another gene, the *regulator,* located elsewhere on the genome. The product of the regulator gene can be modified by specific molecules in the cytoplasm, so that it will activate or suppress, as the case may be, its own operon. This produces a control mechanism whereby the group of genes responsible for a group of enzymes that metabolize a sugar, for instance, will produce the enzymes only when the sugar is present in the environment, thus making the cell more efficient.

GENE MUTATION

A gene, as previously stated, is a reprint of DNA forming the code for a particular polypeptide. Mutation involves an alteration in the code at one particular site, i.e., involving one nucleotide. A single gene, with hundreds of nucleotides, has hundreds of possible mutational sites. Recombination between homologous DNA strands occurs between successive nucleotides at many sites in the DNA strand. Even the concept of the gene as a functional unit cannot be accepted without question, because there are many examples of complex loci, i.e., units that are transmitted as single genes but have more than one recognizable effect.

In general terms, a *mutation* is any sudden heritable change in DNA. A point mutation involves the substitution of one base for another within a triplet. If this substitution alters the codon so that it codes for a different amino acid, the mutation results in a synthesis of an altered polypeptide chain, with an amino acid substitution at a position colinear with the site of the mutation in the corresponding DNA codon. Thus, a given gene locus can exist in one of several different states.

Alternative forms of the same gene are termed *alleles.* Each individual carries two sets of genes, one from each parent. If the two members of a pair of genes are similar, the individual is said to be *homozygous* for this locus; if they are different, the individual is *heterozygous.* A heterozygous individual will make two kinds of mRNA for that gene and two kinds of corresponding polypeptides.

2. The Chromosome

Chromosomes (from the Greek *chromo*, meaning "color"; *soma*, meaning "body") are individually distinguished during cell division, at which time they appear as rodlike bodies. The normal number in the human is 46, and each of the 46 chromosomes is a member of a homologous pair. One member of each pair is received from the mother and one from the father. In both males and females, 22 of the pairs are identical and are designated *autosomes*. The homologous chromosomes in each pair of autosomes are usually indistinguishable. The remaining pair of chromosomes are the *sex chromosomes*. In the female, the two sex chromosomes are identical and are referred to as X chromosomes. In the male, there is an X chromosome and a distinctly different chromosome, the Y chromosome, which is smaller in size than the X and is not homologous to it.

Because females are XX, their reproductive cells can only carry an X chromosome; in contrast, males are XY and produce X-bearing and Y-bearing sperm in approximately equal numbers. Hence, females are referred to as the homogametic sex and males as the heterogametic sex.

Each parent contributes 23 chromosomes to their offspring, one member of each pair. Each sex cell (gamete), whether it is the ovum or sperm, is said to have a haploid (n) chromosome number. In humans, $n = 23$. The cell formed by the fertilization of the ovum and sperm, the zygote, has 23 pairs of chromosomes, or 46; this is the diploid (2n) number. Almost all human somatic cells are diploid.

MEIOSIS

The two major steps of meiosis, the division of germ cells, consist of pairing of the homologous chromosomes and two successive divisions of nuclear material, resulting in cells with 23 chromosomes. The four stages of meiosis are prophase, metaphase, anaphase, and telophase (Fig. 2-1).

First Meiotic Division

Prophase

Prophase is made up of the following five substages:

1. *Leptotene:* The chromosomes become visible and appear to be single threads, although the DNA has already duplicated.
2. *Zygotene:* Each chromosome pairs with its counterpart. The chromosomes are said to be *synapsed* or *bivalents*.
3. *Pachytene:* Each chromosome is now visible as a double strand.
4. *Diplotene:* The two members of the bivalent begin to move apart, except where crossing over has occurred, and the exchange of strands

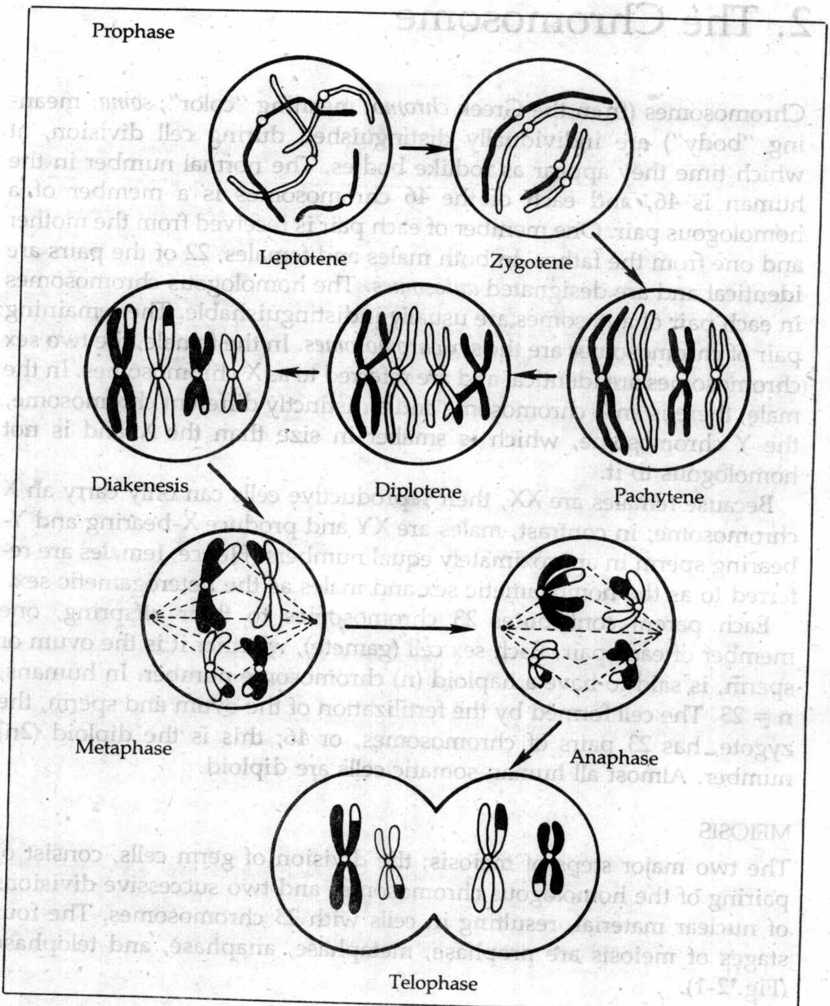

Figure 2-1. First meiotic division.

results in "X-like" formations (chiasmata), which hold the homologues together. Exchanges of genetic material by crossing over adds a very wide variety to the ultimate genetic makeup of a given individual.

5. *Diakinesis:* The final stage of prophase, diakinesis, is characterized by the chromosomes becoming more condensed and darkly staining.

Metaphase

In metaphase, the homologues are paired as bivalents, the nuclear membrane disappears, and the chromosomes line up in an equatorial

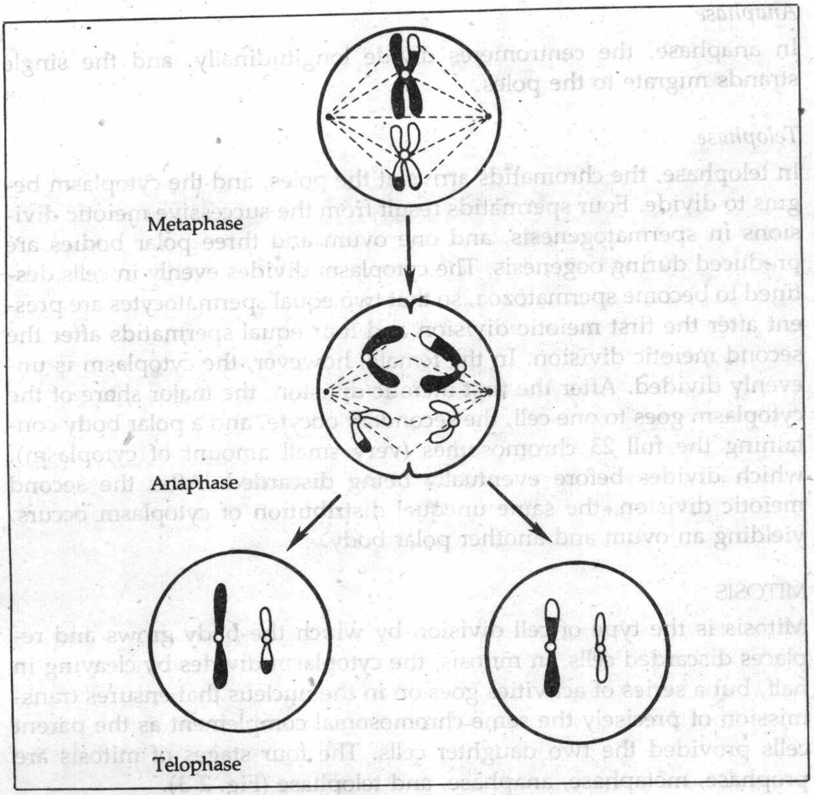

Figure 2-2. Second meiotic division.

plane connected at their centromeres by protein fibers radiating from the centrioles.

Anaphase

In anaphase, the chromosomes separate from their homologous partners, and 23 double-stranded chromosomes go to two daughter cells.

Telophase

In telophase, 23 double-stranded daughter chromosomes conjugate at the poles of the cells.

SECOND MEIOTIC DIVISION

The second meiotic division is illustrated in Figure 2-2.

Metaphase

In metaphase, 23 chromosomes, each consisting of two chromatids joined by a centromere, line up on the equator.