GENETICS IN NEUROLOGY

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Preface

The main goal of this monograph is to emphasize the genetic aspects of neurological disorders. There is no doubt that genetics nowadays should represent an integral part of a neurological work-up. The family history is essential for the understanding of many cases and is often instrumental in establishing the correct diagnosis. The medical history of various family members also aids in the understanding of the natural history of a disease and in recognizing the enormous variability of the clinical expressions of one and the same etiological factor. Moreover, the clinician dealing with a patient afflicted with a genetic or cytogenetic disorder is obligated to assist other family members, current and future, in minimizing the impact of a certain genetic disorder on their lives. A corollary to this obligation is the recognition that in certain instances the focus of health care shifts from the original propositus to other family members. This is what is understood as the "genetic approach" to human disease. It will be an important part of tomorrow's medicine.

The second goal of this monograph is to integrate the biochemical knowledge necessary for the understanding of genetic neurologic diseases. Unquestionably, the biochemical approach will lead ultimately to the solution of many genetic problems. Moreover, development of biochemistry has opened many avenues for the prevention of genetic diseases, such as various gangliosidoses. Particular emphasis is given to bridging the gap between the clinico-pathological approach and basic defects in the metabolic pathways of carbohydrates, lipids, amino acids, and neurotransmitters. Specific problems such as types of inheritance, frequency, heterogeneity of clinical and biochemical phenotypes, somatic cell hybridization, carrier detection, prenatal diagnosis, genetic counseling, and new therapeutic trials, notably with respect to gene product replacement, are reviewed and discussed for more than 200 neurological conditions.

This volume of combined clinical neurogenetics and genetic neuropathophysiology is addressed to a large audience including geneticists, neurologists, neurosurgeons, psychiatrists, psychologists, pediatricians, and medical biochemists, as well as house officers, students in the basic and clinical neurosciences, and researchers in neurobiology.

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Acknowledgments

The authors of this monograph were privileged to receive their medical education under the tutorage of two teachers, both of whom were pioneers in the field of genetics. Victor Ionasescu trained in the Neurological School of George Marinesco, with his pupils Arthur Kreindler, Anghel Radovici, State Draganesco, and Vlad Voiculesco. The contribution of George Marinesco to the description of inherited ataxias, where he identified a new condition characterized clinically by cerebellar ataxia, cataracts, and mental retardation, was outstanding. He also wrote an excellent monograph on the neuron *(La Cellule Nerveuse)*, in which he advocated a morphological and biochemical approach for the understanding of neurological diseases.

Hans Zellweger worked for many years under and with Guido Fanconi, who was one of the first physicians to include in his educational curriculum an extended period at an institute of biochemistry. He introduced the analysis of biochemical parameters into pediatrics, and also contributed to the discovery of such genetic disorders as mucoviscidosis, galactosemia, and X-linked hydrocephalus. Twenty years before the discovery of trisomy 21 as the cause of Down syndrome, Fanconi, in work based on twin studies, predicted the possibility of a chromosomal abnormality for this condition.

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Introduction

Historical Development of Modern Genetics

Heritability of phenotypic characteristics and disorders has been known since time immemorial. Physicians and philosophers of antiquity such as Hippocrates and Aristotle wrote about it and the Talmud (4th century, AD) enounced rules regarding when to do a circumcision and when not to do it, which suggests that its writers already knew about the inheritance of certain bleeding disorders (possibly hemophilia). Researchers, notably botanists of the 17th, 18th, and 19th centuries, concerned themselves with plant hybridization and its results. Galton, a close relative of Darwin, drew attention to twin studies in the late 19th century, as a means for distinguishing between heredity and environment. He wrote also about the heritability of intelligence (7). It was left, however, to the mathematical mind and the astute observations of Gregor Mendel, an Augustinian monk in Brno, Czechoslovakia, to devise the scientifically tenable rules of single gene inheritance. While other geneticists of his time still believed that hereditary traits blended, Mendel—by mathematically analyzing his hybridization experiments with peas—established the laws of independent assortment and segregation of hereditary characteristics. Mendel's work (14), published in 1866, was beyond the understanding of his contemporaries. It remained forgotten until the beginning of the 20th century when its importance was recognized simultaneously by various geneticists, such as Hugo de Vries in Holland (20), Carl Correns in Germany (5), Erich von Tschermak in Austria (19), and William Bateson in England (1). At about the same time, in 1902 Sutton (17) and Boveri (2) identified chromosomes as the carriers of the genetic units or characteristics. The term "gene" did not exist at that time. It was coined in 1909 by the Danish botanist Johannsen (11). Although progress was noticed in subsequent years in plant genetics and cytogenetics, human and medical genetics lagged behind for many decades until it exploded in an unprecedented fashion in the second half of the 20th century. This was brought about by the improvement of the methodology and the introduction of new techniques in cytogenetics, biochemistry, and biophysics. Improved techniques used for chromosome analysis *led* to the discovery of the normal human karyotype in 1956 (18). In 1959, Lejeune and co-workers in France (13) and Jacobs and Strong (10) in England found that mongolism or Down syndrome, is due to the presence of a supernumerary, small, acrocentric chromosome. In the following years, a number of other numerical and

structural chromosome disorders were discovered. Further progress in cytogenetics was reached in the late 1960s when new refined staining methods of the chromosomes were developed (3). By using these new techniques, it became possible to differentiate the individual chromosomes from each other and to identify small structural abnormalities more accurately. A host of structural chromosome abnormalities has been described in the last years. In 1966, the study of the chromosomes of the fetal cells suspended in the amniotic fluid was proposed (16). By combining amniocentesis and chromosome analysis, the prenatal diagnosis of certain chromosome disorders became a reality. Prenatal cytogenetics has since then developed into an important branch of cytogenetics.

The enormous development of methodology used in biochemistry and biophysics had profound repercussions on the development of genetics, notably biochemical genetics and DNA research. In 1902, Garrod described alcaptonuria and coined the term "inborn error of metabolism" (8). Various inborn errors of carbohydrate, amino acid, and lipid metabolism were described in subsequent decades, but the causative enzyme defects were only recognized after 1950. Cori and Cori in 1952 discovered a defect of glucose-6-phosphatase as the cause of glycogenosis type 1 or von Gierke disease (6). La Du et al., in 1958, found that a deficiency of the enzyme homogentisic oxidase was the cause of alcaptonuria (12). Since then innumerable enzyme defects causing various metabolic errors have been identified. Ingram, in 1956, discovered the basic molecular defect of the sickle cell hemoglobin, and a host of other hemoglobinopathies has been identified since then (9).

Successful attempts have been made in recent years to diagnose certain inborn errors of metabolism during fetal life, and scores of disorders can be recognized in the amniotic fluid or in cells suspended therein. Methods to diagnose hemoglobinopathies prenatally are being developed. Attempts have been made to treat inborn errors of metabolism by replacing the missing gene product. Enzyme replacement therapy has hitherto not been successful, although some results have been obtained with enzyme replacement in adolescent or nonneuronopathic Gaucher disease.

To describe the enormous advances that have been made in basic genetics with the discovery of the chemical (4) and structural composition (21,22) of the DNA molecule, the cracking of the genetic code (15), the mapping of genes on the chromosomes, DNA excision and repair, and DNA recombination experiments is beyond the scope of this monograph. It is, however, quite possible that DNA repair will become clinically significant in the not too distant future.

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Chapter 1

A Few Basic Principles of Modern Genetics: Chromosomes and Genes

Chromosomes are the carriers of genetic information, i.e., the genes. A gene can be defined as the unit of the genetic information or as that part of the DNA sequence that codes or transcribes for one genetic information. The chromosomes are located in the cell nuclei. Every nucleus of the billions of somatic cells that make up the human body carries the same chromosomal complement. The gonadal stem cells carry the same genetic complement, whereas the gametes, ova, and sperm, carry only half of the genetic information of the somatic cells and of the gonadal stem cells. They are haploid. Somatic cells and gonadal stem cells have a diploid set of 46 chromosomes, that is, 23 chromosomal pairs; one of each pair is of paternal origin, and the other of maternal origin. One pair represents the sex chromosomes or heterosomes, with males having an X and Y chromosome, and females having two X chromosomes. The X chromosome carries many genes, whereas the Y chromosome carries only a few genes which are mainly concerned with the determination of the male sex during the organogenic period of embryonal life. There are 22 pairs of autosomal chromosomes, which form a fine meshwork of elongated chromatin fibers during the intermitotic or metabolic phase of the cell cycle. During mitosis the chromosomes contract and condense. They are usually studied in the metaphase, when they are optimally contracted and condensed. Metaphase chromosomes have a short arm, a long arm, and a centromere or kinetochore. The short arm is designated by p (p for petit, French for small) and the long arm by q; the centromere keeps the two chromatids together before they segregate in the terminal phase of mitosis.

Chromosomes that have the centromere in the middle of the two arms are called metacentric; chromosomes 1, 3, 16, 19, and 20 are metacentric. Chromosomes that have the centromere near the end of the chromosome are called acrocentric; chromosomes 13, 14, 15, 21, 22, and Y are acrocentric. Acrocentric autosomes have satellites on the end of the short arm, which are attached to the chromosome by a narrowly constricted stalk (secondary constriction). The satellites participate in the formation of the nucleolus, a nuclear organelle concerned with the synthesis of ribosomal RNA. Chromosomes that have the centromere somewhat off the middle

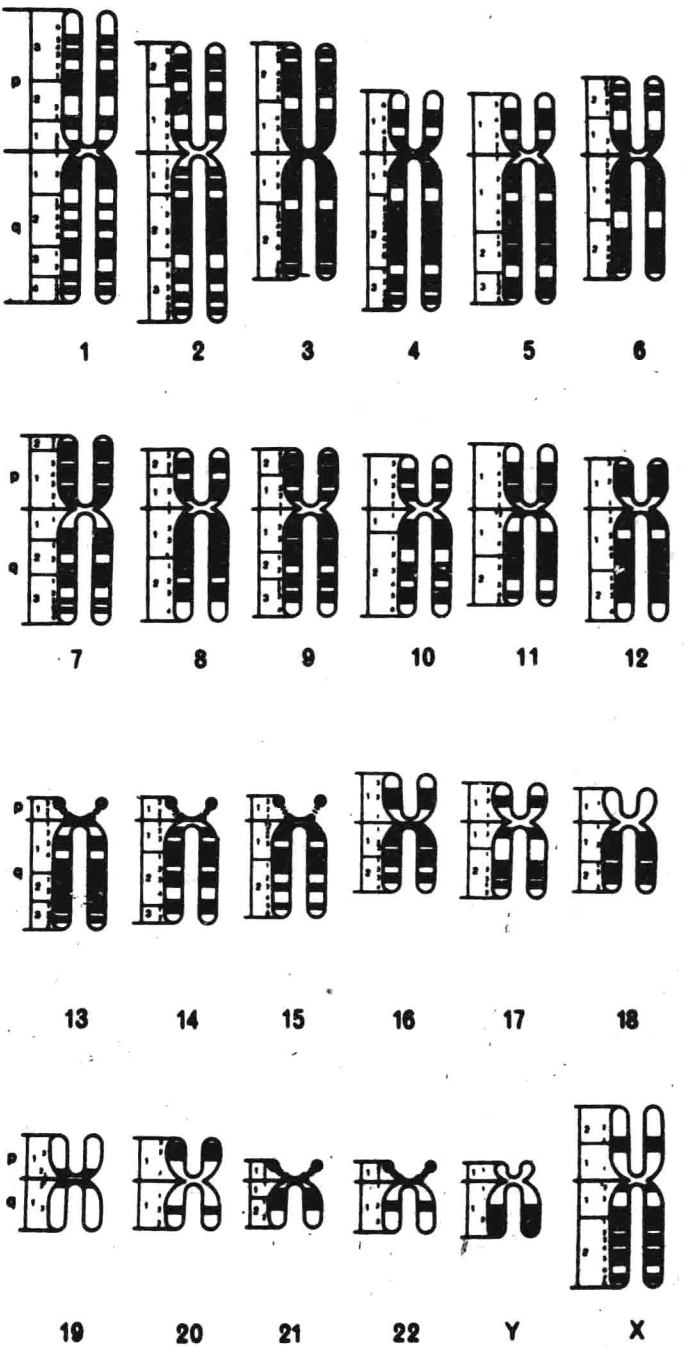
are called submetacentric chromosomes. All chromosomes except those mentioned above are submetacentric chromosomes. The metaphase chromosomes are divided into seven groups, labeled A to G according to their size. Chromosomes of group A are the largest ones, and chromosomes of group G the smallest ones. The autosomal chromosome pairs are numbered 1 to 22.

Group A Chromosomes 1, 2, 3 (meta- and submetacentric)
Group B Chromosomes 4, 5 (submetacentric)
Group C Chromosomes 6–12, X (submetacentric)
Group D Chromosomes 13–15 (large acrocentric)
Group E Chromosomes 16–18 (meta- and submetacentric)
Group F Chromosomes 19, 20 (metacentric)
Group G Chromosomes 21, 22, Y (small acrocentric)

With the staining methods available in the early years of the cytogenetic era the chromosomes belonging to the same group could not always be distinguished from each another, and small structural anomalies were frequently overlooked. In the late 1960s and early 1970s new staining techniques—so-called chromosome banding techniques—were developed, which allowed recognition of the infrastructure of the chromosomes. Chromosomes could now be subdivided into regions, which are delineated by larger bands or landmarks. The regions are again subdivided into smaller bands. Regions and smaller bands within a region are numbered. Regions and bands close to the centromere have lower numbers; those regions and bands with higher numbers are more distant from the centromere (Fig. 1.1); for example, 13q21 indicates small band 1 of region 2 of the long arm q of chromosome 13. By using these banding techniques each chromosome can now be exactly identified and small structural abnormalities (small deletions, inversions, duplications, and reciprocal translocations) are readily noticeable. Small and inconspicuous structural anomalies are even better recognizable if the chromosomes are examined in the prophase, whereby many more (over 1,200) small bands can be distinguished.

The two autosomes of a given pair are homologous as are the two X chromosomes of the female. Genes located at a given site or "locus" of two homologous chromosomes are concerned with the same genetic information. If their information is fully identical, the individual is homozygous for that particular characteristic; if the two genes differ slightly but are still concerned with the same characteristic, the individual is heterozygous. The two genes of a given locus are called alleles or allelomorphic genes. A simple example illustrating allelism is the ABO blood group system. The genes coding for blood group A, B, and O are allelomorphic. A normal euploid individual can have only two of these three alleles.

The allele O does not express itself phenotypically when present in single dose; it expresses itself only if present in double dose, thus O is a recessive characteristic. The alleles A and B do express themselves when present in single dose; thus, they are dominant. A and B are also called codominant, since both express themselves in blood group AB. The allele A has been subdivided into five suballeles A_1, A_2, A_3, A_4, and A_5, the latter being extremely rare. These five alleles differ from each other only quantitatively. They react to the same anti-A antibody, yet with different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intensity. A_1 is dominant over all other A alleles, A_2 is recessive to A_1, but dominant to the other three A alleles, etc. The ABO blood group system represents a simple example of genetic polymorphism. In polymorphisms, multiple alternative forms of the same gene occur at the same locus. Many polymorphisms are known: enzyme polymorphism such as creatine kinase (CK), lactic dehydrogenase (LDH), and glucose-6-phosphate dehydrogenase (G6PD), and protein polymorphism such as various blood groups, and HLA histocompatibility systems. CK has three isoenzymes, LDH has five isoenzymes, and G6PD has nearly 100 isoenzymes. The HLA histocompatibility system is well known for its importance in tissue transplantation. There are nearly 20 alleles on the HLA-A locus, nearly 30 alleles on the HLA-B locus, 6 alleles on the HLA-C locus, and 12 alleles on the HLA-D locus.

As mentioned above, all cells of the most diversified tissues and organs have the same genome, that is, the same genetic information, although the cells may have very different tasks and functions. This suggests that all genes do not transcribe in every cell. Genes whose gene product is not needed for the correct functioning of a particular cell are obviously suppressed or shut off. There must be in each cell a fine regulatory mechanism that controls gene transcription. Moreover, a particular gene can be suppressed and turned on at different times of a person's life. An impressive example represents the appearance and disappearance of various hemoglobins during embryonal (tropho-blastic), fetal (fetal circulation), and postnatal life.

Chromosomes are composed of deoxyribonucleic acid (DNA) supported by histone and nonhistone proteins. The histones are the fundamental structural proteins of the chromosomal organization. The genetic information is carried by DNA. The chemical composition of DNA includes the pentose deoxyribose, phosphate, the purine bases guanine (G) and adenine (A), and the pyrimidine bases cytosine (C) and thymine (T). One base plus one molecule of phosphate and pentose form a nucleotide. The DNA is arranged as a double-stranded spiral, the famous double helix of Watson and Crick.

During cell divisions, the double helix disentangles, and the two DNA strands separate from each other to serve as templates for a new complementary DNA strand. Replication of the two single strands takes place and two new double helices are formed, one for each of the two daughter cells. Replication of the single DNA strands guarantees that every daughter cell originating from mitosis obtains the same genome the parent cell had. In other words, maintenance of the same genome throughout the many generations of cells in our growing organism is the noble task of the replicating, single DNA strand.

Another task is accomplished by DNA during the intermitotic phase of the cell cycle. In order to transmit genetic information to the cell plasma, its ribosomes,

FIG. 1.1. Diagrammatic representation of chromosome bands. □Negative or pale staining Q and G bands; positive R bands. ■Positive Q and G bands; negative R bands. ▨Variable bands. Reproduced from Zellweger and Simpson (1977): *Chromosomes of Man.* Lippincott, Philadelphia. With the permission of authors and publisher.

only parts of the double helix, disentangle and separate to single strands. These then form a template to transcribe the gene information to the messenger RNA. RNA differs from DNA in two respects: Thymine is replaced by uracil and deoxyribose by ribose. The transcription from DNA to RNA is regulated by RNA polymerase, an enzyme originating in the nonhistone portion of the chromosome protein. This enzyme is able to recognize the exact DNA sequence representing a given gene, and in so doing, guarantees the correct transcription of the gene. The second task of DNA is, therefore, to maintain the vital processes within the cell during its metabolic or intermitotic phase by correctly initiating the process of transcription and translation.

The DNA sequence of a gene may undergo alterations that change the genetic information to some extent. This is called mutation or point mutation; the altered gene is called a mutant gene. A subtle example is shown by the mutation of hemoglobin A (HbA) to hemoglobin S (sickle cell hemoglobin), which involves the beta chain of the Hb A molecule, whereby only 1 of the 146 amino acids is replaced by another one. A gonadal mutation becomes inheritable; it can be transmitted through many generations. On the other hand, if a mutation occurs in a somatic cell only, the descended cells of that cell are affected; yet such mutation is not heritable.

There are three main categories of genetic and cytogenetic disorders:

1. Disorders due to numerical or structural abnormalities of the chromosomes (cytogenetic disorders).
2. Disorders caused by a single mutant gene or a single mutant gene pair (monogenic inheritance).
3. Disorders due to multiple genes (polygenic inheritance).

Environmental factors are frequently involved in the causation of polygenically inherited conditions. Thus, some authors prefer to speak of multifactorial inheritance.

Chromosomal abnormalities arise often during the process of cell division. They may occur during mitosis as well as during meiosis.

By mitosis, a somatic cell is divided into two daughter cells that contain exactly the same chromosomal complement as the cell from which they originated. Under normal conditions, the same karyotype is maintained throughout life and through the myriads of mitotic divisions that follow the formation of the zygote. Normal mitosis maintains the normal chromosomal complement within a given individual.

Through meiosis and subsequent amphimixis constancy of the chromosomal complement is maintained throughout the generations. Meiosis consists of two cell divisions by which the diploid complement of the gametic stem cell is reduced to the haploid complement of the gametes: ova and sperm. Amphimixis, i.e., fusion of sperm and ovum, restores diploidy of the zygote and the subsequent somatic and gonadal stem cells. During prophase of meiosis I replication and condensation