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INTRODUCTION

Medical genetics, along with its important area such as clinical genetics, stand out among other scientific disciplines dedicated to the study of human heredity. Nowadays, medical genetics, based on the results of fundamental research in the field of human genetics, can provide answers to three fundamental issues.

Where in the genome disease genes are located?

What is the functional variability of the DNA sequence in these genes?

How to implement the obtained information into clinical practice (diagnosis, prognosis, treatment).

Medical genetics has evolved from a small specialty dedicated to rare hereditary diseases into an important medical specialty, which concepts and approaches have over time become important components of the diagnosis and treatment of many diseases, both rare and common. It has become part of the broader field of molecular and genomic medicine, which uses broad analysis of the human genome, including control of gene expression, human gene variability, and the interaction of genes and the environment designed to improve medical care for patients and their families. In recent years, such new genetic patterns as an expansion of nucleotides, homogeneous disomy, epigenetic regulation, the role of small interfering RNAs have been discovered. Furthermore, hundreds of disease-associated genes have been identified. In fact, we are at the beginning of the revolutionary process of integration of genetics and genomics knowledge into healthcare and medical practice. Genetics is rapidly becoming the organizing principle for medical practice, laying the foundations for personalized medicine.

Future physicians must be prepared to accept new information that genetics brings to light because none of its achievements can be realized in healthcare practice without competent specialists. It is important for a medical student to continuously develop a personal need to master new genetic knowledge.

Since the release of the previous edition, a lot of new information in the field of medical genetics has been accumulated, gained new viewpoints on certain diseases, on the patterns of long-known disease occurrence and development, developed new approaches to prevention and treatment of other diseases besides rare monogenic diseases. All this is reflected in the new edition of our textbook.

A methodological breakthrough in the association studies of genetic polymorphisms and multifactorial diseases in the post-genomic era is reflected in the chapter on “Diseases with a hereditary predisposition”, which describes

the results of the study of molecular mechanisms involved in the pathogenesis of widespread diseases.

In recent years, significant progress has been made in the study of xenobiotic biotransformation genes (metabolism genes), therefore, this edition of the textbook includes new chapters on "Human Ecological Genetics" and "Pharmacogenetics". This information is expected to be the basic knowledge for any physician, primarily for the pharmacogenetic understanding of a personalized approach to drug treatment, and then for ensuring the safety of the human environment: professional activity, particularly those involved in the chemical industry, an individual's diet (toxicogenetics, nutrigenetics).

This textbook summarizes the experience of teaching medical genetics at the departments of the I.M. Sechenov First Moscow State Medical University and the Siberian State Medical University, in Tomsk, Russia. It seems important to us to emphasize that true education is, above all, an understanding of basic principles, and "not memorizing piles of trivial information and subtleties". It is important for future physicians to understand the paradigms of modern genetic science and learn how to apply the acquired principles in their medical practice, and the process of clinical thinking.

The present textbook aims to teach students the language of science, to show the logic of the emergence of new genetic knowledge about the types of pathology (mendelian, chromosomal, multifactorial), to mark what is understood in pathology and what still remains to be clarified by the examples of theoretical and practical lessons at the Department of Medical Genetics.

The authors would like to express their sincere gratitude to students, postgraduate students, and physicians for their interest in the textbook that stimulated thinking about complex genetic processes and presented them in an accessible to a physician way.

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Chapter 1
INTRODUCTION TO CLINICAL GENETICS[1]

BASIC CONCEPTS

Genetics, along with morphology, physiology, and biochemistry, serves as the **theoretical foundation for modern medicine**. Heredity underlies all life's manifestations. Without inheritance and variability, the evolution of life on Earth would be impossible. Since human is the result of the long evolutionary process of living nature, his evolution as the biological specie Homo sapiens reflects all general biological laws.

Human genetics studies the phenomena of heredity and variability at all levels of its organization and existence: molecular, cellular, organismic, populational, biochorological and biogeochemical. Since its inception (the beginning of the 20th century) and especially during the period of intensive development (in the 1950s), human genetics has developed not only as a theoretical but also as a clinical discipline, constantly enriched by both general biological concepts (the theory of evolution, ontogenesis) and genetic discoveries [the laws of inheritance of traits, chromosomal theory of heredity, the informational role of DNA (deoxyribonucleic acid)]. At the same time, the development of human genetics as a science has been constantly and significantly influenced by the achievements of theoretical and clinical medicine. A human as a biological object has been studied in more detail than any other highly organized organism (drosophila, mouse, etc.). The study of pathological variations (the subject of the medical profession) became the basis for studies of human heredity. In turn, the development of human genetics has accelerated the development of theoretical disciplines (for example, molecular biology) and clinical medicine (for example, a new field in medicine, the studies of chromosomal disorders).

Medical genetics is concerned with the role of heredity in human pathology, the patterns of genetic disease transmission across multiple generations,

[1] It has been corrected and supplemented with the participation of I.N. Lebedev, Dr. of Sci. (Biology).

the development of methods for the diagnosis, treatment, and prevention of hereditary pathology, including diseases with a hereditary predisposition.

The discoveries and research achievements in the areas of medicine and genetics are aimed at combating diseases and improving human health.

Medical genetics, as the most important part of theoretical medicine, is concerned with the following issues related to pathology:

- what hereditary mechanisms maintain the homeostasis of the body and determine the individual's health status;
- what is the significance of hereditary factors, either mutations or a combination of certain alleles, in the disease etiology;
- what is the ratio of hereditary and environmental factors in the disease pathogenesis;
- what is the role of hereditary factors in the manifestation of the hereditary and non-hereditary diseases;
- whether does the hereditary constitution affect (and if it does, how) the process of a person's recovery and the outcome of the disease;
- how heredity determines the specificity of pharmacological and other types of treatment.

Medical genetics as a theoretical and clinical discipline continues to develop rapidly in distinct ways: genomics, cytogenetics, molecular and biochemical genetics, immunogenetics, developmental genetics, population genetics, clinical genetics, pharmacogenetics, environmental genetics, nutrigenetics, and toxicogenetics.

The syllabus in medical genetics includes the basics of general genetics (Mendelism, the chromosome theory, the chemical basis of heredity), the basic provisions of human genetics (a person as an object of genetic research) and clinical genetics.

Clinical genetics is an applied branch of medical genetics. Its achievements are applied in clinical problem solving when dealing with patients or their families. Clinical genetics can provide answers to the following issues: what kind of disease the patient has (diagnosis), how to help him (treatment), how to prevent the birth of affected children (prognosis and prevention), how to assess and reduce the risks of developing a disease with a hereditary predisposition. Currently, clinical genetics uses, on the one hand, genetics techniques (genetic analysis, molecular biological, cytogenetic, biochemical, immunogenetic) and, on the other hand, all modern methods of clinical examination [ultrasound imaging (sonography), magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET)].

A BRIEF HISTORY OF MEDICAL GENETICS

Pre-Mendelian period

The theory of human heredity began within the medical field with empirical observations of family and congenital disorders. The role of heredity in the disease's origins was already referred to in Hippocrates writings: "... epilepsy origin, like that of other diseases, lies in heredity. For if a phlegmatic parent has a phlegmatic child, a bilious parent a bilious child, a consumptive parent has a consumptive child, and a splenetic parent a splenetic child, there is nothing to prevent some of the children suffering from this disease as well when one or the other of the parents suffered from it".[1] However, for the next few centuries, the interest in the role of heredity in the disease origins was lost, instead, in the theories of medicine, the priority was given to external etiological factors. Some single works dedicated to the importance of heredity in the disease origins (polydactyly, hemophilia, albinism) only appeared in the 18th and 19th centuries.

The concept of human pathological heredity arose in the second half of the 19th century and was adopted by many medical schools.

Along with the notions of pathological heredity, arose the need to improve the concept of the degeneration of the human race, which was announced in Russia by V.M. Florinsky and in England by F. Galton, simultaneously (1865) and independently (Fig. 1.1, 1.2).

In the 19th century, the prerequisites for the development of the theory of human heredity stemmed from biological discoveries that revolutionized medicine: cell theory (T. Schwann) and evidence of cellular continuity (R. Virchow); notions of the idea of onto- and phylogenesis; explanation of evolution by natural selection and the struggle for existence (Charles Darwin). General medical prerequisites had no less influence on the theory of hereditary diseases than biological discoveries. In the 19th century, the study of the disease causes of has become a priority in the field of medicine.

The period of the definition of certain diseases as nosological units including hereditary ones has begun. For example, have been described Down syndrome, neurofibromatosis, congenital connective tissue dysplasia, etc. The studies of pathological symptoms were replaced by the studies of nosological forms of diseases, which could be traced in genealogies as discrete forms.

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[1] *W.H.S. Jones translation* (slightly changed).

Fig. 1.1. V.M. Florinsky (1834–1899), a Russian obstetrician-gynecologist and pediatrician. He is the author of the book entitled "The Improvement and Degeneration of the Human Race" (1865). The founder of the first educational institution in Siberia — Tomsk State University (1880–1888)

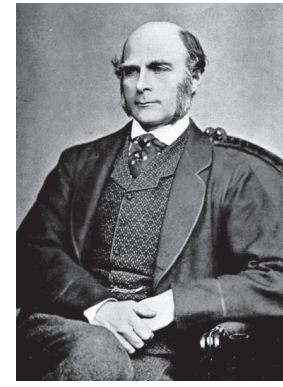

Fig. 1.2. Francis Galton (1822–1911), one of the founders of human genetics and eugenics. His major works in this area are: "Hereditary talent and character" (1865); "Hereditary genius: a study of its laws and consequences" (1869); "Essays on Eugenics" (1909)

Although in the 19th century, the theory of hereditary diseases and the laws of human heredity advanced significantly, in general, many contradictions remained. Most of the works of this period mixed facts and misconceptions. Criteria for the correct interpretation of the inheritance of diseases did not yet exist. Human genetics was at a "pre-scientific" stage of development. This **period** can be referred to as **pre-Mendelian**.

The discovery of Mendel's laws

Only in 1900, with the rediscovery of Mendel's laws, those unique opportunities for the inventory of hereditary diseases emerged in this field. Mendel's laws were confirmed first by one and then by other real case examples from physicians and biologists. Inheritance as an etiological category has become firmly established in medicine. The nature of many diseases has been understood.

For example, at the very beginning of the 20th century, in accordance with the patterns of inheritance of traits discovered by Mendel, English physician A. Garrod explained the hereditary nature of a rare metabolic disorder named autosomal recessive alkaptonuria. Moreover, he explained other biochemical abnormalities by the idea he expressed in the book entitled "Inborn errors of metabolism" (1909). After that, he was recognized as the father of biochemical genetics.

In the first two decades of the 20th century due to the euphoria generated by the Mendelian interpretation of many diseases, the role of heredity in human behavior and the hereditary burden of human populations was significantly exaggerated. The theory of the doom and degeneration of the families with hereditary pathology has become the dominant one to explain the burden on society with the offspring of such patients. The diagnosis of a hereditary disease was considered a sentence to the patient and even to his family. Under these circumstances, **eugenics**, a scientific movement attempting to improve the breed (or nature) of mankind (positive eugenics is the preferential breeding of individuals with positive qualities) previously formulated by F. Galton, began to gain momentum.

The understanding of negative eugenics was limited to that part of it that sets as its goal the liberation of humanity from individuals with hereditary pathology. Eugenics ultimately "justified" the forced restriction of reproductive freedom. Therefore, it is more correct to consider eugenics as a social or mass movement rather than a science.

Eugenics is one of the examples of the unjustified widespread introduction of unverified results into practice (dizziness from success). Generally, it played a negative role in the development of both genetics and biomedical science. The history of Russian eugenics is detailed and objectively described in the books of E.A. Pchelov and V.V. Babkov (see "Recommended literature").

In the 1920s

Human genetics continued to evolve. The use of Mendelism and the chromosomal theory of heredity (formal genetics) brought about an understanding of the general patterns of hereditary pathology, the causes of clinical polymorphism, genetic heterogeneity, a recognition of the role of the external environment in the development of diseases with a hereditary predisposition.

In the 1920 and 1930s Russian medical genetics developed successfully. First, mention should be made to the most valuable contribution of S.N. Davidenkov, Russian geneticist and neuropathologist (Fig. 1.3), who is regarded as the founder of the national clinical genetics. He dedicated himself to the study of genetics of neurological diseases and determined the work on general genetic issues for several decades. He was the first in the world who suggest creating a catalog of human genes, to formulate the concept of the genetic heterogeneity of hereditary diseases, and to organize a medical genetic consulting service.

Fig. 1.3. S.N. Davidenkov (1880–1961), a geneticist and neuropathologist. He is regarded as the founder of clinical genetics in the USSR. He was the first in the world to suggest creating a gene catalog (1925), organized the world's first medical genetic counselling service (1929). He is the author several books on the genetics of inherited diseases of the nervous system: "Hereditary diseases of the nervous system" (1st edition in 1925, 2nd edition in 1932); "The problem of polymorphism of hereditary diseases of the nervous system" (1934); "Evolutionary and genetic problems in neuropathology" (1947)

The development of medical genetics supported I.P. Pavlov. In the 1920s, he began to study the genetics of higher nervous activity.His role in the development of medical genetics is described by N.P. Bochkov in his "Article about I.P. Pavlov".

In the 1930s – 1940s

In the period between 1930 and 1937, crucial role in the development of medical genetics played by Medico-Biological Institute, which in 1935 was renamed as the Institute of Medical Genetics. It was an advanced institution that conducted high level twin and cytogenetic studies. Unfortunately, the institute was closed, while its director, prof. S.G. Leviticus, has undergone repressions (Fig. 1.4).

In the 1930s, genetics has firmly and widely rooted in medical science and practice. The most accurate medical significance of genetics for that period was unraveled by I.P. Pavlov (1935): "Life requires the utmost application of the laws of inheritances discovered by Mendel. Genetic postulates have been sufficiently studied and may be intensively applied. The laws of heredity should become the ABC of our physicians. The implementa-

Fig. 1.4. S.G. Leviticus (1894–1937), a director of the Medico-Biological Institute, which in 1935 was transformed into the Institute of Medical Genetics. He supervised the scientific research in the several fields of human genetics (cytogenetics, twin studies, clinical genetics, formal genetics)

tion of the postulates and laws of inheritance in life will help to save humanity from many sorrows and grief".

In the 1950s – the end of the 20th century

The most effective period in the development of human genetics began in the 1950s. In 1959, after the discovery about the chromosomal nature of diseases, cytogenetics became the dominant field of medicine for several years. During this period, clinical genetics emerged from the fusion of three branches of human genetics: cytogenetics, formal (or Mendelian) genetics, and biochemical genetics. The human being has become the main object of general genetic studies. The interaction of genetics and medicine led to huge breakthrough in the study of human heredity and the implementation of its results in practice.

It was precisely in the 1960s when the Russian medical genetics resumed its development. The older generation of geneticists and scientists of related disciplines (V.D. Timakov, S.N. Davidenkov, V.P. Efroimson, A.D. Prokofieva-Belgovskaya, E.F. Davidenkova, S.A. Malinovsky, E.E. Pogosyants, N.N. Medvedev, Yu.Ya. Kerkis) has actively contributed to its revival. Founded in Moscow in 1969 the Institute of Medical Genetics of the USSR Academy of Medical Sciences, in 1989 was renamed as the All-Union Research Centre for

Medical Genetics of the USSR Academy of Medical Sciences (now the Medical Genetic Research Center of the Russian Academy of Medical Sciences).

At the turn of the 20th and 21st centuries, medical genetics has become dominant in life sciences bringing together advanced methods and concepts from different medical and biological disciplines.

Various circumstances contributed to the intensive development of medical genetics in the second half of the 20th century. After the Second World War, due to the decreased levels of infectious and nutritional diseases, more attention began to be paid to diseases of an endogenous nature including hereditary ones. The progress in the fields of laboratory and instrumental medicine, a wide exchange of information insured a more accurate "nosologization" of syndromes and diseases. The progress in the areas of general genetics and biology has cardinally changed the methodology of human genetic studies (molecular biology, cytogenetics, genetics of somatic cells).

The main achievement of medical genetics by the end of the 20th century was the creation of genetic technologies that allowed us to quickly solve problematic issues in medicine and health care (Table 1.1).

Table 1.1. Genetic technologies in medicine and healthcare

Area of medicine	Area-specific issues
Theoretical	Deepening the disease inventory by nosological principle. Deciphering the pathogenesis of diseases. Causes of clinical polymorphism. Causes of chronic diseases. Pharmacogenetics
Clinical	Diagnostics of hereditary and infectious diseases. Pathogenetic treatment of hereditary diseases. Production of genetically engineered drugs. All types of prevention of hereditary diseases
Preventive	Genetic and hygienic rationing of environmental factors. Prevention of mutagenic, teratogenic, and carcinogenic effects. Development of new vaccines

The contemporary advances in human genetics require from physician new ways to learn. This statement of the 1980 Nobel Prize laureate P. Berg is especially relevant at the present time, when, within the scope of an international project, the human genome has been sequenced and mostly decoded, while molecular medicine laid the basis of clinical and preventive medicine:

Just as our present knowledge and practice of medicine relies on a sophisticated knowledge of human anatomy, physiology, and biochemistry, so will dealing with