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Review

The Centenary Progress of Molecular Genetics. A 100th Anniversary of T. H. Morgan's Discoveries

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A B S T R A C T

A century ago, Thomas Hunt Morgan, the American scientist, studied the cytogenetic changes of drosophila and came to cytogenetic explanation of Mendel's basic laws of genetic heredity. These studies resulted in today's Mendel-Morgan chromosomal theory of heredity. On the occasion of the hundredth anniversary of this important discovery the authors have decided to give a review of the most significant achievments in the field of molecular genetics until the completion of the Human Genome Project. The most important points concerning the technology of DNA recombination and genetic engineering are also presented. The final section discusses the significance of previous achievements of molecular genetics in biomedicine and other related fields. There is also a tabular presentation of the sequence of the most important findings in the field of molecular genetics through time.

Key words: *history, T. H. Morgan, molecular genetics, genetic engineering*

Introduction

»PCR is the most important new scientific technology to come along in the last hundred years.«
C.R. Hughes, 2001

The significance of heredity in inheritance of different bodily characteristics, as well as in the occurrence of disease has been described from the very beginnings of medical history. Biologists and many other scientists have devoted their efforts to the understanding of the transfer of hereditary traits, as well as the physical and chemical properties of the related processes. Gregor Johann Mendel (1822–1884), a highschool teacher and Benedictine priest, is considered the founder of traditional genetics. Working in the St. Thomas monastery in Brno he performed numerous experiments on various plants and animals. In his experiments he also used green beans and, formally being a physicist, he applied statistical analysis for the first time as a scientific approach. He noticed that when cross-bred, the offspring of plants inherit certain traits in strict numerical orders. In his work »Versuche über Pflanzen – Hybriden«, published in 1866, he states that many characteristics are transferred to offspring by certain »hereditary factors«. Furthermore, he stated that young plants inherit one »factor« from each parent, who actually have a double »hereditary factor«. Therefore, according to the fundamental Mendel Law on Heredity, a single entity inherits two »factors« for each trait, called alleles, which can be identical or different and are manifested in the development of the entity[1,2].

Mendel's research, published in the not so popular publication »Verh. Naturforsch. Verein Brünn«, passed unnoticed, and it was only in 1900 that the botanists, Hugo de Vries, in the Netherlands, Carl E, Correns in Germany, and Erich von Tschermak in Austria, brought to wider attention Mendel's assumptions and provided further evidence of their significance. Namely, in 1901

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Hugo de Vries published his finding that individual organisms had the characteristics that their ancestors did not have and were the variations caused by spontaneous changes of hereditary traits, called mutations. He referred to the newly formed organisms as the mutants[1,3].

The development of a microscope and laboratory equipment enabled the scientists to learn that all cell nuclei contained the substance called chromatin,that turns into denser and visible pairs of chromosomes during cell mytosis. These stained fibre-like corpuscles observed in dividing living cells were described in 1882 by Walter Flemming. He was also able to confirm that, during cell fertilisation, the offspring received the haploid number of chromosomes from the gametes of both parents[4].

In 1902 Walter S. Sutton, the American scientist, finally provided proof that, as assumed by Mendel, the chromosomes behaved as »factors« during cell division and emphasized the relation between chromosomes and inherited traits.

The English mathematician Geoffrey H. Hardy and German ophthalmologist and geneticist Wilhelm Weinberg described in 1908 the relation between the frequency of alleles and the frequency of genotype in a single site – which is today referred to as Hardy-Weinberg equilibrium[5].

Thomas Hunt Morgan and co-workers at the New York Columbia University provided evidence regarding genes as units of heredity and their strict alignment in regular sequence along the chromosome. Morgan experimented on fruit flies (*Drosophila melanogaster*), which were most appropriate for study purposes since they require less than 14 days for new progeny. By observing hereditary changes of white and red eyes, small and large wings, and similar traits in the drosophila, Morgan concluded that genes were linearly aligned in proximity one to the other (linkage), but even so during the transfer they could separate and get into new units individually. Thus the chromosome of a new entity contains the collection of linked and independent genes which are all inter-related (linked genes) and most often commonly inherited. Furthermore, Morgan discovered that the offspring sometimes inherited only single genes from a chromosome and that single genes were sometimes cross-transferred from one chromosome to the other – the transfer referred to as crossing over. The results of Morgan's studies became essential in the construction of first genetic maps[3,6,7].

By studying chromosome localisation and linear sequence of genes, as well as their mutational capacity, Morgan provided a cytogenetic explanation of Mendel's observations and clarified the mechanism of heredity involved in fertilisation, leading to, what is nowadays referred to as Mendel-Morgan chromosomal theory of heredity.

Further research was aimed at discovering the position of genes in a cell nucleus, i.e. in chromosomes. In 1913, Alfred H. Sturtevant, a student of Morgan, described linear sequence of genes in chromosomes. It was also confirmed that during cell division (mitosis) the number of chromosomes doubled and that from these pairs the newly created cells received one segregated chromosome.

In 1921, Theophilus Shickel Painter, the American zoologist, by studying human sperm cells during meiosis discovered that each contained 24 chromosomes. Later one of his students concluded that the oocyst contained the same number of chromosomes, whereas all other human body cells should contain 48 chromosomes. This observation remained the subject of dispute for nearly three decades[1,4].

During almost twenty years the scientists have paid close attention to the nature of genes. Besides biologists, many physicists and chemists have studied and clarified fundamental biochemical events occurring within cells. These studies focused on amino acids, lipids, simple carbohydrates, but also larger so-called macromolecules such as nucleic acids and proteins. The studies also included molecular regulation of biological processes in cells, genetic information contained in the studied molecules and the ways in which transformation of the genetic data into chemical reactions results in certain phenotypic traits and ensures biological homeostasis of the organisms[3].

The American geneticists George W. Beadle and Edward Lawrie Tatum in 1941 revealed that single genes determined the production of enzymes and that the segments of deoxyribonucleic acid (DNA) served as the matrix for the formation of protein molecules in the cell.

Working at the New York Rockefeller Institute in 1944, Oswald Theodore Avery, Colin MacLeod and Mechin McCarty studied the transformation of pneumonia bacillus and proved that genetic messages are contained within DNA molecules located in chromosomes that segregate during mitosis, and that it is only the DNA that determines heredity. Consequently, these studies are considered as the beginning of the period of molecular genetics[1–3].

In 1950 Erwin Chargaff in his studies of the arrangement of nucleotide bases showed that the DNA molecule consist of four acid bases, showing a constant proportion of purine and pyrimidine bases, i.e. adenine and thymine, guanine and cytosine[1].

Alfred Hershey and Martha Chase in 1952 showed that viral penetration into bacterium leads to transfer of solely DNA molecules, followed by multiplication of many new viruses within the bacterium. This finding confirmed the previous assumption regarding the transfer of genetic informatioan via DNA, i.e. the chemical transfer of hereditary traits.

These study results stimulated many scientists to begin new research of the chemical structure of genes and soon it was established that the DNA molecule is formed by a nitrogen base, deoxyribosis and phosphate group.

The British scientists Maurice Hugh Frederick Wilkins and Rosalind Elsie Franklin have in 1953 studied the crystallographic structure of partially dehydrated and crystalline DNA molecule by diffraction of X-rays and have shown that the double polynucleotide chain has

a spiral shape (helix) turning around the central axis. Purine and pyrimidine bases are located in the helix at 0.34 nm distance between them. Based on spatial relations between atoms Wilkins has calculated the DNA density and also that the DNA molecule contains more than one polynucleotide chain in the form of a helix[8–10].

In 1953 James Dewey Watson, the American zoologist, and Francis Harry Compton Crick, a British physicist, summarized the data of chemical and X-ray studies and eventually came to perhaps the most important discovery in the field of genetics: the identification of the structure of deoxyribonucleic acid (DNA). They described the three-dimensional structural DNA model with pairs of four nitrogen bases: adenine (A), guanine (G), thymine (T) and cytosine (C), arranged and linked in the form of a double helix resembling a ladder. The rungs of the ladder are formed by pairs of bases linked with hydrogen bonds, namely adenine with thymine and guanine with cytosine. During cell mitosis the DNA helix divides lengthwise segregating the base pairs; the bases of each half of the helix bind with the corresponding free base and form pairs identical to the original ones. Watson and Crick wrote the following: »Our model of deoxyribonucleic acid is a pair of complementary matrices and we assume that the hydrogen bonds break prior to doubling, while the two chains separate and unwind. Thus each chain becomes a matrix of its own on which new helix is formed, eventually producing two pairs of chains in the site where there was only one, and the sequence of base pairs is exactly doubled.« The discovery contribute in clarification of the question of DNA transcripts during cell mitosis and explained how the information stored in DNA molecule can get correctly transferred to both progeny cells and cell organelles that produce proteins. Namely, each chain in the helix equals in a mirror-like fashion the complementary DNA chain and after the separation it transfers identical messages to both new cells[11–14].

The same year, Frederick Sanger, a British chemist, elaborated the first procedure for determining and sequencing of DNA arrangement by deducting the hydroxyl group on 3' end and on 2' position of deoxyribose, by which the joining of the next nucleotide is prevented. Fitting of such a molecule, called dideoxynucleoside, into the developing DNA molecule inhibits further synthesis of the DNA chain[1].

Interestingly enough, it was only in 1956 that the findings of Joe Hin Tjio and Albert Levan in Lund made it possible to definitely understand the diploid number of 46 chromosomes in human cell. Namely, they finally confirmed that the entire complement of genetic material is contained in 22 autosomal pairs and one gonosome, i.e. within 46 chromosomes. At international conferences in Denver 1960, London 1963 and Chicago 1966, the system of identification and classification of human chromosomes was agreed upon. Based on the decrease in size and position of centromere during metaphase the chromosomes were divided into seven groups: from A to G[4,15].

Arthur Kornberg, the American biochemist, in 1957 extracted in vitro the DNA from Escherichia coli bacterium. He mixed the DNA segments with specific enzymes and added them to the matrix of the natural DNA; the result was that the segments of DNA were joined into chains identical to the DNA matrix. Ten years later Kornberg produced a biologically active DNA capable of natural reproduction. The DNA polymerase I enzyme, that catalyses phosphodiester bonding of nucleotides in a 5' to 3' direction, is referred to as Kornberg enzyme, in honor of his achievements. It recognizes the pentose-phosphate part of the molecule thus enabling the determination of specific sequences of nitrogen bases. Accordingly, the DNA polymerase I is active only when DNA molecule is present determining the sequence of nucleotides during the synthesis of a new chain. It should be added that the DNA polymerase II and DNA polymerase III, the most important enzymes in the polymerisation process, have also been isolated from Escherichia coli[7,16,17].

In 1958 Matthew Meselson and Frank Stahl expanded upon the Watson and Crick's discovery by the so-called model of semi-conservative synthesis. Namely, they argued that both new DNA molecules are »hybrids« of the original and the newly created chain. They cultured *Escherichia coli* bacteria in a medium with a heavy nitrogen isotope (^{15}N) and the newly developed DNA molecules ($^{15}N/^{15}N$) were heavier than the DNA molecules cultured in a medium with standard nitrogen (^{14}N). They could be separated by centrifuging them in the density gradient of cesium chloride (CsCl). Subsequently, after plasing them in the medium with normal nitrogen (^{14}N) the heavier DNA molecules synthesised hybrid DNA molecules ($^{15}N/^{14}N$) and in the next bacterial generation the DNA molecules contained one original light chain ($^{14}N/^{14}N$) and one newly developed hybrid chain ($^{15}N/^{14}N$). Further culturing increased the number of light DNA molecules and eventually resulted in two hybrid and two light nucleotide chains preserving the parent polynucleotide sequence in DNA molecules of the offspring[1,17].

Many studies of biochemical processes involved in DNA synthesis in cells followed and from 1961 to 1965 many scientists tried to fully reveal genetic information, in the sequences of DNA molecules. Today it is clear that the DNA macromolecule transmitting hereditary traits is determined by the sequence of nucleotides. Each nucleotide is formed by one of the four nitrogen bases to which sugar bonds with five carbon atoms (pentose-deoxyribose) and a phosphate group are added laterally. Two bases are purine: adenine (A) and guanine (G), and two are complementary pyrimidine ones: cytosine (C) and thymine (T).

Marshall W. Nirenberg and Heinrich J. Matthaei, American biochemists, in 1962 identified the genetic code for phenylalanine amino acid, while in the following years their colleagues identified genetic codes for all twenty amino acids involved in protein synthesis. Eventually it was possible to identify how DNA directed the expression of proteins and what role RNA had in these processes.

In 1964 Charles Yanofski, the American biologist, and his colleagues, through studying genetic mutations in Escherichia coli bacteria, showed that the arrangement of nucleotides in DNA molecules directly influences the sequence of amino acids in proteins.

Marshall W. Nirenberg and Gobind Har Khorana included other scientists in their research and at the beginning of 1960s they could show that genetic transcripts consists of a triple structure of nitrogen bases (triplet code; codon), e.g. AAT, AAC, and each determines one amino acid in a protein. In a DNA molecule the codon acts via the complementary molecule of the messenger ribonucleic acid (mRNA) that has copied the DNA sequences, whereas the consequent strands of transfer ribonucleic acid (tRNA) synthesized proteins. Such transfer of information leaves the DNA intact and is elementary to the fundamental law of molecular biology – the central dogma[1,18].

Based on the overall research and study results, molecular biologists eventually came up with two fundamental concepts: the genetic code and the central dogma (principal theorem).

The genetic code instruct that the sequence of bases determines the information needed for incorporation of specific amino acids into proteins, bearing in mind that a single DNA molecule can contain thousands of genes.

The central dogma indicates that the sequential information of nitrogen bases in a DNA molecule is transcribed into RNA molecule as a message for protein formation. Thus, according to Crick the basic pattern is the following: DNA › RNA › protein, with specific sequence of events pertaining to RNA as follows: mRNA, rRNA, tRNA.

The central dogma has been amendment when American scientists David Baltimore and independly Howard M. Temin in 1970 discovered reverse transcriptase, derived from retroviruses, that can synthesize a cDNA strand from an RNA template.Furthermore, in the 1960s the French scientists showed through their experiments on Escherichia coli that individual proteins can activate or inhibit specific genes[2,7,18–20].

Roger D. Kornberg in 1974 described the mechanism of chromatin summarization, i.e. the structure of nucleosomes with the DNA strands containing from 146 to 200 pairs of nucleotide bases surrounding the histones (the histone octomere with two H2A, H2B, H3, H4). Kornberg also explained and provided a detailed presentation of the transformation of the genetic code into tRNA molecules[16,17].

It has been known for a long time that identical genetic codes can be found in different parts of DNA molecule and that many DNA parts do not confer genetic information. However, the studies of Richard Roberts and Philip Sharp (1977) were the first to identify that the DNA molecule contains exons, sequences carrying genetic information, and introns, which separate exons and do not convey genetic informatio[18,21].

The full understanding of the genetic code sequences was achieved through the results of three most important discoveries in 1980s and 1990s.

Sidney Altman and Tom B. Cech with co-workers recognized in early 1980s that the 28S, 18S and 5S RNA ribosomes (the so-called PRE-rRNA) have fundamental impact on the formation of proteins, mainly through catalyzing numerous processes within a cell, including polymerisation and replication of nucleotides[1,17].

In 1977 Frederick Sanger from Cambridge and Walter Gilbert from Harvard produced the breaking of the polynucleotide DNA chain and inhibition of synthesis of the DNA chain by implanting the dideoxyribonucleoside 5[1]-triphosphate, thus developing the the enzymatic method of DNA sequencing. In this way the correct sequencing of A, T, G and C nitrogen bases in DNA was enabled and their original procedures are considered fundamental to the decoding of the human genome[22,23].

David Botstein and co-workers in 1980 reported small variations in the genomic material and indicated that a new type of genetic markers, Restriction Fragment Length Polymorphism – RFLP, first described by Ray L. White, could serve for design of a polymorphic marker map in genetic analyses[6].

In 1983 Robert Tjian, William Dynan and afterwards James Kadonga described linked DNA segments (GC box sequence) to which specific proteins are bound (Sp1) which stimulate transcriptions in vitro. Such synthetic oligonucleotides were used as probes for target sequences[1, 17].

Alec J. Jeffreys and associates published in 1985 their key discussion on sequences of limited repeats duration, called minisatellites. This lead to the introduction of DNA analysis using the so-called Multi-Locus Probe system (MLP), commonly referred to as DNA fingerprints in today's forensic medicine[24–26].

Yusuke Nakamura and collaborators in 1987 discovered the existence of multiple minisatellites, i.e. loci, called Variable Number of Tandem Repeats – VNTR[27].

Kary Banks Mullis at the same time improved the DNA replication procedure by which it was possible to reproduce extremely small DNA molecules in vitro. The discovery of Polymerase Chain Reaction – PCR has enabled the analysis of biological samples containing very small amounts of DNA. It is interesting to note that Mullis designed the concept of PCR while driving a car in the night through the Californian mountains in1983[28–30].

The term microsatellite appears for the first time in reference literature in 1990s. Initially it was used only for repeated CA/GT dinucleotide motifs, while other terms were used for tandem repeats, simple sequences and short tandem repeats (STR). Today the term microsatellite is generally used for all sequences of short motif repeats, including the microsatellites and cryptically simple regions (CSR). Microsatellites are defined as sequences not longer than six nucleotide bases with tandem repeats without interruptions by other motifs. Also, the microsatellites show a high degree of polymorphism,

whereas the microsatellite loci amplified by PCR procedure also contain interruptions[31–33].

Yechezkel Kashi and co-workers have shown in 1997 that microsatellite sequences have the functional role of coding or regulatory elements and are found in the origins of promoter regions of coding sequences. It has also recorded that the capacity of protein binding and stimulating effect of microsatellites depends on the number of tandem repeats in specific microsatellite spaces.

Yechezkel Kashi and David G. King have further explained the finding that microsatellites can be an important source of quantitative genetic variations and consequent evolutional adaptation[34,35].

During the second half of the 20th century the geneticists also focused on the possibilities of rearrangement and transfer of genetic material, i.e. the recombinant DNA technology.

Following Barbara McClintock's pioneering studies (1956) on mobile, i.e. transposable genetic elements and the ability of genes to change their positions in chromosomes, Robert Holliday in 1064 designed the procedure of slicing single chains of two DNA molecules and bindings their severed ends, the procedure nowadays referred to as the initial model of DNA recombination.

In 1969 Chris Graham, a Philadelphian scientist, showed the possibility of fusion of somatic cells with unfertilized egg cell, which in vitro developed to the stage of morula.

In 1970 Werner Arber, a Swiss scientist, and Hamilton O. Smith and Daniel Nathans, American scientists, investigated the possibility of cutting out specific sequences from DNA molecules by restriction endonucleases laying the groundwork in the field of recombination of DNA molecules.

Following these studies, Derek Bromhall managed to successfully transfer the cell nucleus into an egg cell and thus opened the path to cloning of cells. In 1971 C. Merril, M. Geier and J. Petricciani proved in Bethesda that genes transferred from a phylogenetically distant organism can in the cytoplasm of new host form proteins coded by the imported genetic message[1,36,37].

Stanley Cohen and Herbert Boyer in 1973 improved the procedure of gene transfer using plasmids – very small bacterial round DNA molecules.

Paul Berg, the American scientist, with his colleagues eventually in the late 1970s elaborated the possibility of transfer of single genes from one entity into the another – the process commonly referred to as genetic engineering[1,38].

In 1984, working at the Philadelphia Wistar Institute, Jim McGrath, a scientist from U.S.A., and Davor Solter, a Croatian scientist, discovered that paternal and maternal genes in a zygote were not functionally identical. They have also shown the existence of a minute group of 100 to 200 genes in which only one allele is active -the so-called imprinted gene. Consequently, during gene reprogramming changes and disorders can take place. The process that determines the activity of a gene is referred to as epigenetic inactivation of the alleles, i.e. parental imprinting[39].

In the past three decades genetic engineering has made it possible for scientists to investigate in greater detail the genetic structure and activities of more complex plants and animals. This has contributed to better understanding of numerous biological events and has eventually enabled the deciphering of the human genome. Rapid development of molecular genetics and new generations of gene cloning vectors, together with the use of modern technologies have lead to development of high-throughput sequencing methods. The Sanger enzymatic procedure is still in use with minor modifications and improvements, with automation and computerisation contributing to greater accuracy and increased efficacy[38].

Combined efforts of many scientists resulted in 1987 in the foundation of the International System of Gene Nomenclature – ISGN by Thomas B. Shows, and in 1989 started a colossal project commonly known as The Human Genome Project. The project was organized by two American institutions: the National Human Genome Research Institute and the U.S. Department of Energy. Simultaneous efforts aimed at harmonization of terminology related to DNA markers in 1995 resulted in the establishemnt of the National DNA Bank in Great Britain. In the United States in 1997 was also established Combined DNA Index System – CODIS[40].

Finally on February 15th, 2001, the International Human Genome Sequencing Consortium – IHGSC, including about 2500 scientists from all over the world, declared the completion of the Human Genome Project. The study carried out by Francis S. Collins as the principal study director and scientists from twenty leading American, British, Canadian, German, French, Japanese and Chinese laboratories. Among other outcomes, the proclamation of The Universal Declaration on the Human Genome and Human Rights should be emphasized, sinc eit granted unlimited access to the project database and content. Almost at the same time the scientists from the Celera Genomics, with Craig J. Venter as principal investigator, published their version of the map of the human genome. In contrast to previous projections, the studies have shown that the human genome contains roughly twenty five thousand structural genes responsible for protein coding, as well as several hundred genes for non-ptoein RNA[40–42].

The field of human genetics has witnessed significant advancements in the past few years. New insights into the biological processes have been established mainly through the development of novel scientific disciplines, such as genomics, proteomics and metabolomics. The progress in genomics has enabled decoding of nucleic acid sequence for many organisms. Following successful decoding of human genome the scientific effort in the post-genomic era is firstly aimed at the complete characterization of all genes in the human cell at the level of proteins and metabolites. The growing complexity of biomedical research, however, demands a multidisciplinary

TABLE 1
SIGNIFICANT EVENTS IN THE DEVELOPMENT OF MOLECULAR GENETICS

Year	Researcher	Finding	Nobel prize
1866	G.J. Mendel	Versuche über Pflanzen-Hybriden, Verh. Naturforsch. Verein, Brünn 4,3–47	
1882	W. Flemming	Presentation of chromosome development	
1900	H. de Vries, C.E. Correns E. Tschermak	Confirmation of Mendel's Law	
1901	H. de Vries	Studies of mutations	
1902	W. Sutton	Correlation between chromosomes and heredity	
1903	W. Johannsen	The terms gene and genotype	
1906	W. Bateson	Linkage between different »factors« on chromosome; the terms genetics and phenotype	
1908	G.W. Hardy	The assumption of the balance in the frequency of W. Weinbergalleles and genotype; Law of balance	
1910	T.H. Morgan	Genes are the units of heredity and aligned along the chromosome; Chromosomal theory of heredity	1933
1913	A. Sturtevant	Linear alignment of genes in a chromosome	
1927	H.J. Muller	Mutation of genes caused by X-rays	1946
1938	W. Weaver	The term molecular biology	
1941	G.W. Beadle	Genes are segments of DNA and they determine E.L. Tatumenzyme formation	1958
1944	O.T. Avery,	Gene messages are transcripted in DNA molecules C. MacLeod, M. McCarty	
1950	E. Chargaff	Constant proportion of four purine (AT) and pyrimidine (GC) bases in a DNA molecule	
1952	A. Hershey,	DNA is the carrier of hereditary messages M. Chase	1969
1953	M. Wilkins et al.	Crystallographic structure of DNA molecule R. Franklin et al.	1962
1953	J.D. Watson,	The structure of DNA molecule like a double helix F.H.C. Crick	1961
1953	F. Sanger	The procedure of protein sequencing	1958
1956	B. McClintock	The ability of genes to change their positions within chromosomes (transposition); mobile genetic elements	1983
1956	J.H. Tjio	Human cell contains 46 chromosomes A. Levan	
1957	A. Kornberg,	The first DNA polymerase and DNA product in vitro S. Ochoa	1959
1958	M. Meselson,	The model of semi-conservative synthesis F. Stahl	
1958	F.H.C. Crick	The triplex code-codon	
1961	F. Jacob, J. Monod	Coding of enzymes that harmonize and direct the mRNA transcription – operons and operators	1965
1961	S. Brenner, F. Jacob, M. Meselson	Genetic control of enzymes and messenger mRNA	2002
1961	F.C. Crick et al.	The coding triplet of nucleotides – codon	
1962	M.W. Nirenberg, H.J. Mathaei	Transcript for amino acid phenylalanine	
1964	M.W. Nirenberg, G. Khorana	The triplet code (codon) acts via mRNA	1968
1964	R. Holliday	The model of cutting and crossing di-molecule chain of DNA recombination	
1965	S. Brenner et al.	The nonsense »stop« codon	
1968	R.W. Holley	The real structure of tRNA	
1968	R. Okazaki et al.	The permanence of the newly synthesised DNA parts in small segments	
1968	A. Kornberg et al.	Manufacture of biologically active DNA	
1970	D. Baltimore R. Dulbecco H. M. Temin	Reverse transcriptase that can synthesize a cDNA strand from an RNA template	1975
1970	W. Arber, H.O. Smith, D. Nathans	Cutting out sequences of DNA molecule by restriction endonuclease	1978

1971	C. Merril, M. Geiger, J. Petricciani	The transplanted genes form proteins coded by the transmitted genetic message	
1972	P. Berg et al.	Implantation of foreign DNA and connection of segments	1980
1973	S. Cohen, H. Boyer,	Transfer of genes by using plasmids as vectors	1986
1974	R. Kornberg	Chromatin summation mechanism and structure of nucleosome	2006
1977	F. Sanger et al. W. Gilbert et al.	Enzyme breaking and stopping of DNA chain synthesis and sequencing of restriction segments of A, T, G and C nucleotide bases	1980
1977	T.B. Cech, S. Altman	The effect of rRNA in polymerisation and replication of nucleotides	
1977	P. Sharp, R. Roberts	Identification of information-relevant sequences (exons) and irrelevant sequences (introns) in a DNA molecule	1993
1980	D. Botstein et al. R. L. White	Restriction Fragment Length Polymorphism	(RFLP)
1983	R. Tjian, W. Dynan	Chromatographic purification of specific protein sequences – probes for target DNA sequences	
1984	J. McGrath, D. Solter	Epigenetic inactivation of paternal and maternal alleles – parental imprinting	
1985	A.J. Jeffreys et al.	Minisatellite loci as DNA prints fingerprints	
1987	Y. Nakamura et al.	The loci of Variable Number of Tandem Repeats (VNTR) sequences	
1987	K.B. Mullis, M. Smith	The procedure of small DNA molecules replication – Polymerase Chain Reaction *(PCR)*	1993
1987	T.B. Shows et al.	International system of genetic nomenclature (ISGN)	
1987	C. Nusslein-Villard	The presence of cluster genes that control body development	1995
1989	M.Litt J.A. Lutty J.I. Weber, P.E. May	Terminology and use of microsatellites	
1991	G. Edwards	The term Short Tandem Repeats (STR)	
2001	F.S. Collins	The study of human genome (IHGSC)	
2001	C.J. Venter	The map of human genome (Celera Genomics)	

approach and team-work, which will enable translation from basic scientific discoveries to clinically applicable procedures and treatment.

Significant advances in molecular genetics, half a century after the discovery of DNA structure and only nine years following the completion of the Human Genome Project, have become the foundation for new insights into the genetic background of hereditary diseases, congenital malformations, neoplasm's, chronic and even infectious diseases. In the near future molecular genetics will probably enable their early diagnosis, prevention and treatment. For example, molecular biologists have identified many oncogenes that participate in normal regulation of mitotic cell division, but which can, in exceptional situations, when stimulated by either viruses, chemical substances or some other factors, produce undesired effects. Additionally, many studies are being carried out worldwide regarding the possibilities of genetic therapy, namely by introduction of healthy genes into cells of people with genetic disorders.

Besides biomedicine and agriculture, the future research will definitively stimulate industrial development, as well as progress in many other important fields of human activities. Nevertheless, extreme caution is necessary, since results of the forthcoming biomedical studies might yield social consequences of frightening proportions, comparable to the discovery of atomic energy and use of the atom bomb[7,26,29,40,41].

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STOLJETNI PROGRES MOLEKULARNE GENETIKE

S A Ž E T A K

Američki znanstvenik Thomas Hunt Morgan prije stotinu godina je istraživanjima sa drosophilom ostvario citogenetsko obrazloženje Menedelovih temeljnih zakona, te genskog nasljeđivanja, pa danas govorimo o Mendel-Morganovoj kromosomnoj teoriji nasljeđivanja. Autori su u povodu obljetnice izložili povijesni pregled najvažnijih otkrića u području molekularne genetike, do završetka projekta ljudskog genoma.Pri tome su u kratkome odjeljku prikazani i najvažniji podaci o tehnologiji rekombiniranja DNA i genetičkom inženjerstvu.U završnom odjeljku autori ukazuju na značenje dosadašnjih dosega molekularne genetike u biomedicini i drugim djelatnostima.Naposlijetku je slijed najznačajnijih spoznaja molekularne genetike i tablično prikazan.