Bruno DALLAPICCOLA – Giuseppe NOVELLI

Fundamentals of Medical Genetics

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Bruno DALLAPICCOLA – Giuseppe NOVELLI

Translation by Camilla Gagliardo

Edizioni Scientifiche Falco

Edizioni Falco srl
info@edizioniscientifichefalco.it

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To our alumni,
current students,
and future scholars.

Summary

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Presentation

Two years after the publication of the fourth Italian edition of our Medical Genetics textbook, we have responded to the numerous requests from colleagues and students to produce an English version of the treatise. The goal is to provide a teaching tool capable of offering basic and up-to-date elements of our discipline, accessible even to students in courses not strictly related to the health professions.

The simple yet rigorous language of this volume, significantly reduced in content and images, provides the necessary tools to understand modern Medical Genetics and its impact on human health.

The genetic revolution has profoundly impacted not only medicine and biology but also social, economic, and cultural disciplines such as psychology, law, archaeology, paleontology, sensor technology, bioinformatics, statistics, and bioeconomics. Therefore, scholars in these fields must integrate fundamental human and medical genetics knowledge into their curricula.

This book is aimed at readers interested in learning the basic aspects of Genetics and reflecting on its recent developments, with the conviction that everyone should perceive it, not as a detached observer, but as a potential user.

Bruno Dallapiccola
Giuseppe Novelli

Authors

Bruno Dallapiccola

Physician, Full Professor of Medical Genetics, has primarily conducted his academic activities at the Universities of Urbino, Tor Vergata, and La Sapienza in Rome. He has served as Scientific Director of the IRCCS Hospital Casa Sol- lievo della Sofferenza in San Giovanni Rotondo, the Mendel Institute in Rome, and the Bambino Gesù Pediatric Hospital (OPBG). He is Emeritus Scientific Director of the OPBG. He has been a member of the National Bioethics Committee, the Superior Health Council, and numerous Technical Tables of the Ministry of Health. He founded and was President of the Italian Society of Human Genetics (SIGU) and the Pediatric Network of IRCCSs. He represented Italy on the European Union Committee of Experts on Rare Diseases (EUCERD). He coordinated the Working Group 8 on rare diseases in the European One Million Genomes project. He is responsible for the Italian interface of Orphanet, the world's leading database on rare diseases. He is the author of over a thousand international publications, primarily focused on rare or very rare diseases, which have concerned clinical genetics, the identification of new diseases, the study of genotype-phenotype correlations, and the mapping and cloning of over 50 disease genes

Giuseppe Novelli

Biologist, Full Professor of Medical Genetics at the Faculty of Medicine and Surgery of the University of Rome "Tor Vergata" and Director of the U.O.C. Medical Genetics Laboratory at the Policlinico Universitario Tor Vergata. Adjunct Professor at the University of Nevada, School of Medicine, Reno, (USA).

He has taught at the Faculties of Science and Pharmacy of the University of Urbino and the Catholic University of the Sacred Heart, Rome. He was Dean of the Faculty of Medicine and Surgery of the University of Rome "Tor Vergata" from 2008 to 2011 and Rector of the same University from 2013 to 2019. He has been President of the National Observatory of Health Professions at the Ministry of University and Scientific Research and a member of the Board

of Directors of ANVUR (National Agency for the Evaluation of Universities and Research) from 2010 to 2013. He is currently Director of the School of Specialization in Medical Genetics at the University of Rome Tor Vergata. He is President of the Lorenzini Foundation, Milan. Member of numerous National and International Scientific Societies including the Academia Europaea. He is the author of over 700 international publications concerning the discovery of Mendelian genes associated with genetic diseases in humans, the genetics of complex traits such as psoriasis, myocardial infarction, and susceptibility genes for infectious diseases such as tuberculosis, AIDS, and COVID-19. Professor Novelli's laboratory is currently working on innovative models of cellular and molecular therapies.

Chapter 1
Historical Overview

Genetics, the science that studies hereditary variations in humans, and Medical Genetics, which analyzes its applications in clinical practice, have assumed increasing importance in studying human diseases. While in the past the interest of Medical Genetics was focused only on a limited number of pathologies, today it concerns almost all diseases, both of pediatric and adult interest. Most human diseases have a genetic component. Understanding their biological basis has therefore become a priority in modern medicine

The main impact of Medical Genetics on human health concerns disease control through diagnosis and prevention. The therapy of hereditary diseases is still unsatisfactory but constantly expanding, and looks with increasing interest at the prospects offered by gene therapy and cell therapies, and more generally, by "precision medicine" aimed at counteracting the effects of specific molecular targets.

The central intervention of Medical Genetics towards patients and their families is entrusted to Genetic Counseling (see Chapter 10), which consists of communicating information related to diagnosis, prognosis, and treatment of diseases of interest, recurrence risks, and available prevention. The term "revolution" is often used to describe the extraordinary development of our understanding of genetics in recent decades. At the beginning of the 20th century, Mendel's laws were rediscovered, and clarified the mechanisms underlying the hereditary of simple traits; human chromosomes could be recognized, albeit with difficulty under an optical microscope, but their number had not yet been defined; molecular biology had not even been imagined. Today, over 20,000 simple traits are known, many of which are associated with specific diseases. Chromosomes can be analyzed with sophisticated high-resolution platforms, the genome can be sequenced and examined in a few hours, and personalized medicine, based on individual genomic characteristics is becoming a reality.

Genetics has become a discipline of broad interest for all scientific disciplines, and it is easy to predict that its impact in medicine will increase further in the coming years. This places it at the forefront of research and makes it a fundamental subject in the training curricula of medical students and professionals.

From Origins to Mendel

The milestones in the history of medical genetics have accelerated quite recently. However, it is legitimate to think that, ever since the appearance of *Homo sapiens* on the planet (50,000-200,000 years ago), our ancestors showed interest and curiosity in heredity, mainly based on birth and occasional family recurrence of people affected by congenital defects. We have evidence of this dating back to the pre-dynastic period of ancient Egypt (5,500-3,100 BC). Some dwarfs, like Seneb, who lived between the 4th and 5th dynasties, and the dwarf Djeho (Figure 1.1), an achondroplastic dancer about 120 cm tall, whose image was carved on a granite sarcophagus dating back to the dynasty of King Nectanebo II (362-360 BC), had taken on prominent roles in the public life, and for this reason were buried near the pyramids.

The lack of knowledge about certain events, such as conception, reproduction, and development, did not allow, at that time, to understand the mechanisms responsible for congenital defects. Numerous Greek philosophers and physicians, such as Aristotle, had tackled the issue of the origins of life, attributing a predominant role to male seed, considered the dynamic germinal element capable of conferring the "form", while the "substance" would have been provided by the menstrual blood, considered a kind of culture medium. The uterus would have had the functions of an incubator. According to this theory, the seed would have been produced by the whole body, and this seemed to explain why, for example, children of a balding father would develop the same characteristics. This suggestion, although contested by many others who theorized the "doctrine of the two seeds", found widespread acceptance until the 17th century, when Leeuwenhoek and de Graaf discovered the existence of spermatozoa and

Figure 1.1 - *Achondroplastic dwarf Seneb with his wife Senetiti and their children (circa 252 BC). B. Achondroplastic dwarf Djeho (circa 350 BC).*

oocytes, explaining why certain maternal characteristics could be present in children.

In the 18th and 19th centuries, there was a renewed interest in the problem of heredity. Among others, the studies of Pierre de Maupertius (1698-1759), an eclectic mathematician, geologist, naturalist, and academician, deserve a special mention. He studied albinism and polydactyly, demonstrating that these two conditions were inherited differently. In England, Joseph Adams, a physician, published in 1814 a "Treatise on the Supposed Hereditary Properties of Diseases", differentiating between some disorders that we now define as "dominant" or "recessive". Moreover, he introduced the definition of "congenital" (something present at birth), highlighted a correlation between consanguinity and the onset of certain diseases, introduced some new concepts such as "founder effect", "incomplete penetrance", "variable age of

onset", suggested the importance of the environment in the origin of certain diseases, and recommended the establishment of registries to prevent them. Unfortunately, he could not provide scientific explanations for the ideas he proposed and, for this reason, was ignored by his contemporaries. Nevertheless, he can probably be considered the first clinical geneticist.

A fundamental contribution to the understanding of the genetic basis of heredity was provided by the studies of the Austrian monk Gregor Mendel (1822-1884) who, in 1865, presented at the Natural History Society of Brünn (now Brno in the Czech Republic), the results of some research on controlled crosses of peas, which were then published the following year in the proceedings of the same Society. However, these studies remained ignored until 1900, when they were re-evaluated and have since been considered the first experiments to document the existence of genes and their mechanisms of transmission.

However, the term "gene" was coined only a few years later (1909), by the Danish botanist Ludvig Johannsen, who borrowed it from "pangen", used by the Dutch naturalist Hugo de Vries to indicate the individual physical units. In turn, de Vries borrowed this term from "pangenesis", a theory proposed by Charles Darwin, which later proved to be incorrect, according to which

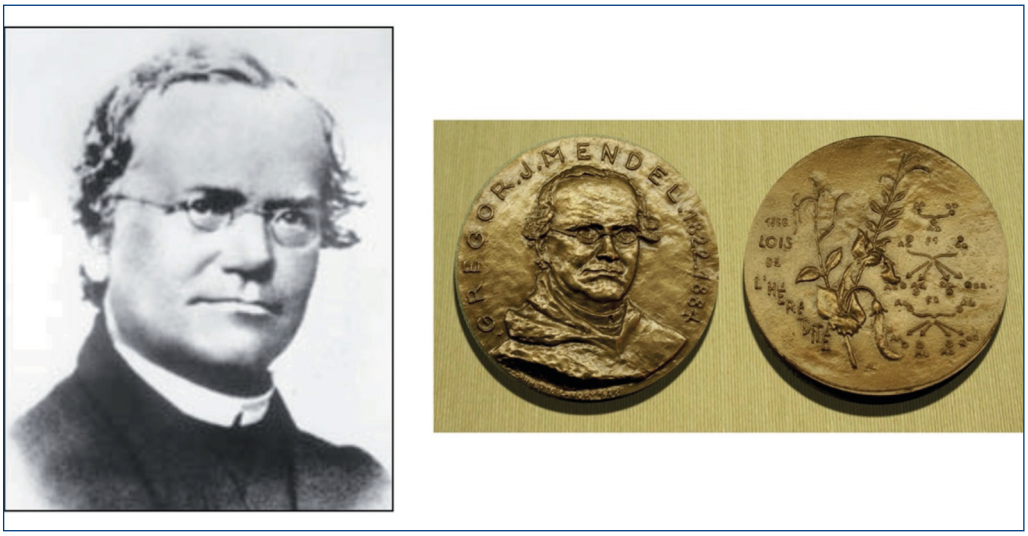

Figure 1.2 - *Gregor Mendel (1822-1884), also depicted in a commemorative medal.*

the germ cells of the parents would receive from the whole (from the Greek "pan") the organism's tiny particles (gemmules), which, once merged, would contribute, in the genesis of the offspring, to the hereditary transmission of the characters acquired by the organism during its life.

In recognition of Mendel's studies, the term "Mendelian" is now widely used to indicate the patterns of inheritance of simple (monogenic) traits, i.e. those that originate from variations in single genes. The concepts of "dominance", i.e. a trait that is expressed in individuals who have only one copy of the mutated gene, and "recessivity", i.e. a trait that is expressed only in the presence of two copies of the mutated gene, derived from the results of pea crosses, apply to Mendelian diseases, similarly to the terms "allele" (from the Greek "allelos", each other), which defines each variant of a gene, in a "homozygous" condition (subject who possesses two identical alleles) or "heterozygous" condition (subject with two different alleles).

After Mendel

The rediscovery of Mendel's laws sparked a widespread interest in the mechanisms of trait' inheritance. At that time, it was already known that cells possess a nucleus, within which, under special conditions, chromosomes can be identified. Chromosomes were named based to their affinity for certain dyes ("chroma" = color; "soma" = body).

In 1903, two independent studies, one by the American medical student Walter Sutton and the other by the German biologist Theodor Boveri, suggested that genes were aligned on chromosomes. This hypothesis was based on the observation of chromosome behavior during cell division (Figure 1.3), which seemed to explain the modes of gene segregation.

Determining the modal number of chromosomes in human cells had to wait many more years, until 1956, when Joe Hin Tjio and Albert Levan fixed it at 46. Only three years later, Jerome Lejeune identified in Down syndrome the first example of a chromosomal disease in humans, trisomy 21. The study that allowed to establish DNA as the hereditary material dates back to 1944. It was a revolutionary result, as until then it was believed

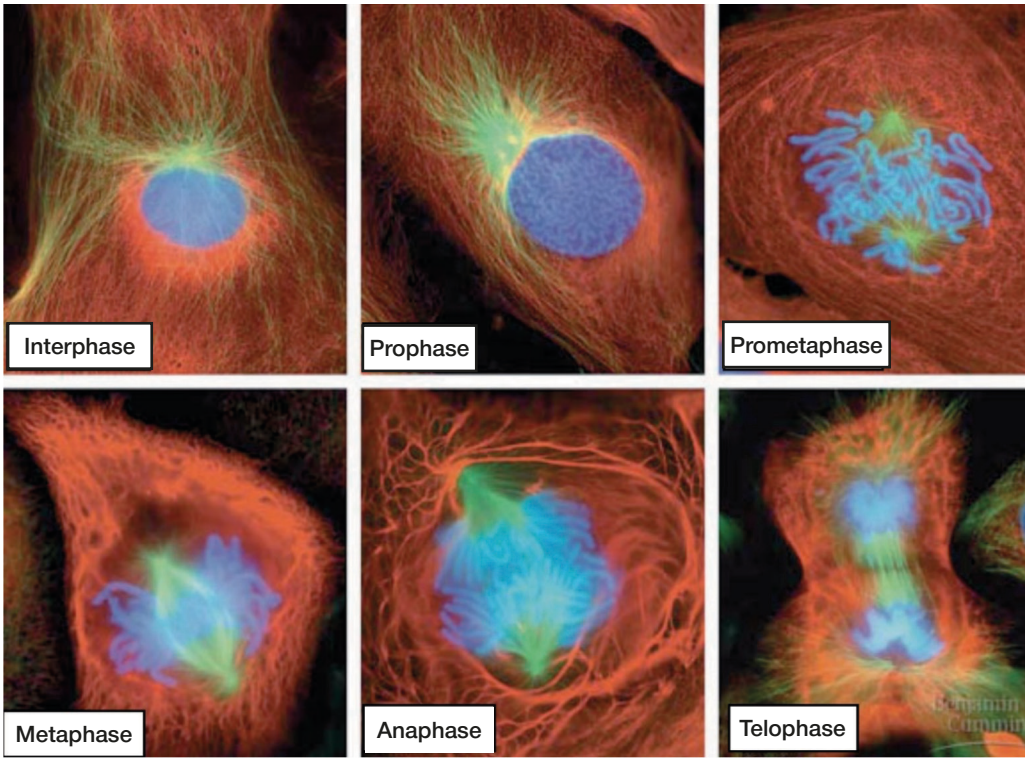

Figure 1.3 - *Phases of cell division and symmetrical distribution of chromosomes in daughter cell.*

that hereditary traits were transmitted by proteins. Nucleic acids had been discovered almost a century earlier (1849) and in 1928 Frederick Griffith, an English biologist, by studying two strains of streptococci, demonstrated that the characteristics of one strain could be transferred to the other, through something he then defined as a "transforming principle". In 1944, Oswald Avery, Maclyn McCarty and Colin McLeod, working at the Rockefeller Institute in New York on pneumococcal strains, came to the conclusion that the bacterial transformation was produced by transfer of a deoxyribonucleic acid molecule. However, this result had left many skeptics, as the molecule in question is relatively simple, with many repetitions of four nucleic acids.

The X-ray crystallography analysis of DNA, conducted at King's College London by Maurice Wilkins and Rosalind Franklin, proved crucial for the subsequent work of James Watson and Francis Crick, who defined the

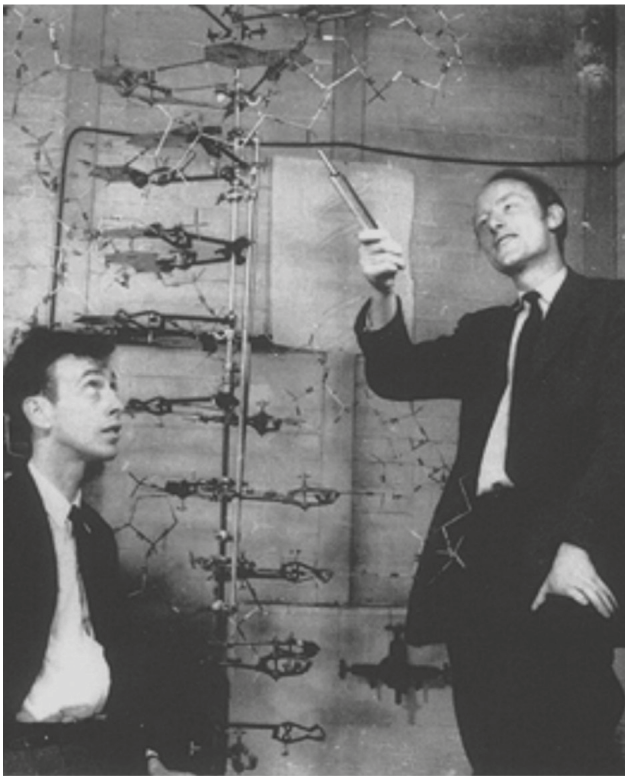

Figure 1.4 - *Watson and Crick and the model of the double helix, Oxford 1953.*

double helix structure of DNA (Figure 1.4). The relationship between the sequence of bases in DNA and the sequence of amino acids in proteins, in fact the genetic code, was clarified by a series of biochemical experiments conducted in the 1960s. These studies allowed the prediction of amino acid changes in proteins, based on mutations in DNA, which were formally demonstrated only a few years later, when, following the introduction of recombinant DNA techniques, sequencing techniques became available. However, even before these methods became available, in 1957 a human disease, sickle cell anemia (Figure 1.5), caused by the modification of an amino acid in hemoglobin, had been characterized at the molecular level, using a complex procedure for sequencing the purified protein.

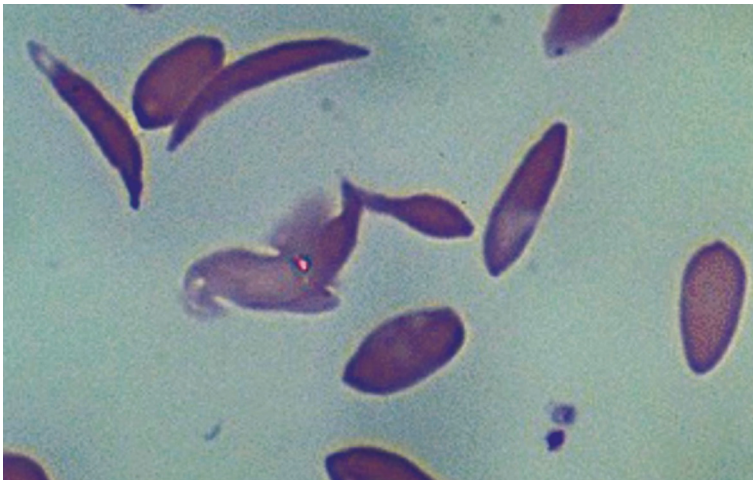

Figure 1.5 - *Peripheral blood smear of a subject affected by sickle cell anemia.*

Origins of Medical Genetics

John Dalton (1766-1844), the inventor of modern chemistry and the first to formulate the atomic theory, also lent his name to color blindness, a condition from which he suffered. He understood the hereditary mechanism of this disease, as well as hemophilia (X-linked inheritance). However, like his contemporaries, Joseph Adams, and his predecessor, Pierre de Maupertius, these founding fathers of Medical Genetics limited themselves to speculate about the mechanisms responsible for the disorders they had investigated. The beginning of Medical Genetics can therefore be more realistically dated to 1900, when, independently, three botanists, Carl Correns in Germany, Hugo de Vries in the Netherlands and Eric von Tschermak in Austria, rediscovered the Mendel's experiments and gave new impetus to the study of hereditary diseases.

William Bateson, a researcher who, among other things, first proposed the term "genetics," and the physician Archibald Garrod are credited with identifying the first monogenic disease, alkaptonuria, a rare, recessive condition related to an alteration in the catabolism of an essential amino acid, phenylalanine. Today it is known that alkaptonuria is caused by an enzyme defect, as a result of which a metabolite, homogentisic acid, accumulates in the urine of affected individuals, which oxidizes easily

giving them a characteristic dark color (so-called ochronosis). After understanding that alkaptonuria was a hereditary disease that affected a chemical process, Garrod coined the term "inborn error of metabolism," which today identifies several hundred conditions assimilated into the chapter of biochemical genetics. Almost a century passed (1902-1996) between the clinical description of alkaptonuria and the identification of the disease gene (HDG).

The first half of the 20th century was characterized by intense experimental and theoretical activity. Various organisms, such as Drosophila melanogaster (a fruit fly) and Neurospora crassa (a bread mold), were used as models to analyze the action and interaction of genes. For example, Hermann Joseph Müller (1890-1967), an American Nobel laureate geneticist, demonstrated the consequences of ionizing radiation in Drosophila, while an English statistician-mathematician, Ronald Fisher (1890-1962), an English geneticist, John Burdon Sanderson Haldane (1892-1964), and an American geneticist, Sewall Wright (1889-1988), laid the theoretical foundations for "population genetics". In the same years, the hereditary mechanisms of other diseases, such as phenylketonuria, Huntington's disease, and cystic fibrosis, were defined.

In the second half of the 20th century, the idea that most diseases had a genetic basis and that various mechanisms were involved in determining these clinical conditions became established. Extraordinary technological developments, particularly in molecular biology, allowed the identification of the genetic bases of thousands of diseases (Table 1.1). In 1990, the "Human Genome Project" was launched (the term genome refers to all the DNA present in an organism), the most ambitious international scientific project ever conceived, which in 2000 allowed the first draft of the genomic sequence to be obtained (Figure 1.6), which was completed in subsequent years, by using complex computer analysis tools, granting the processing of the vast amount of data generated by the project. The number of genes, about 20,000, was significantly smaller than the estimates of about 100,000, which were indicated before the start of the project, while interindividual variability (1-3%) was higher than originally hypothesized. Likely, epigenetic modifications (alterations of gene regulation through chemical processes that

Table 1.1 – *Some significant milestones in the progress of Medical Genetics.*

Year	Milestone	Scientists
1839	Cell theory	Schleiden and Schwann
1859	Theory of evolution	Darwin
1865	Inheritance of simple traits	Mendel
1877	Observation of chromosomes under a microscope	Flemming
1902	Biochemical variability	Garrod
1903	Chromosomes carry genes	Sutton and Boveri
1910	Birth of the first genetics clinic in America	Davenport
1911	Localization of the first human gene	Wilson
1916	X-linked inheritance	Bridges
1927	Effect of ionizing radiation in Drosophila	Muller
1944	DNA as hereditary material	Avery
1953	Structure of DNA	Watson and Crick
1956	Humans have 46 chromosomes	Tjio and Levan
1959	Trisomy 21 and Down syndrome	Lejeune
1960	Prenatal sex diagnosis	Tiis and Fuchs
1961	Biochemical screening	Guthrie
1961	X chromosome inactivation	Lyon
1964	Genetic code	Nirenberg
1966	Chromosome diagnosis	Breg and Steel
1970	Prevention of hemolytic disease of the newborn (Rh isoimmunization)	Clarke
1970	Chromosome banding	Caspersson
1970	Restriction enzymes	Nathan and Smith
1970	In vitro gene synthesis	Khorana
1973	HLA and disease association	Terasaki
1977	Cloning of a human gene	Shine
1978	Production of a protein by genetic engineering	Itakura
1978	Restriction fragment length polymorphisms (RFLP)	Kan

To be continued →

1978	Molecular prenatal diagnosis	Kan
1979	In vitro fertilization	Edwards and Steptoe
1985	DNA fingerprinting	Jeffreys
1985	Polymerase chain reaction (PCR)	Saiki
1987	Human chromosome linkage map	Various authors
1990	First gene therapy (ADA)	Rosenberg, Anderson, Blese
1991	Start of the Human Genome Project	Various authors
1997	Cloning of a mammal	Wilmut
2003	Completion of the Human Genome Project	Collins, Venter et al.
2005	Publication of Phase I of the HapMap Project	Various authors
2007	Publication of the first human sequence	Venter et al.
2007	Reprogramming of adult human cells	Yamanaka
2008	Non-invasive prenatal diagnosis on maternal blood	Chu/Fan et al.
2010	Construction of the first "artificial cell"	Venter et al.
2010	Demonstration of the efficacy of ivacaftor in cystic fibrosis	Ramsey et al.
2012	Diagnosis based on exome sequencing	Saunders et al.
2013	Gene editing with CRISPR-Cas9	Hwang et al.
2014	$1,000 genome analysis	Illumina Co.
2017	Gene therapy for hemophilia and sickle cell anemia	Ribeil/Rangarajan et al.
2018	Conclusion of the Pan Cancer Atlas project	NIH
2018	First immunotherapies	Ott/Sahin et al.
2018	Polygenic risk scores for complex traits	Khera et al.
2018	Start of the All of us and 1 Million Genomes projects	NIH USA and EU
2022	Complete human genome sequence	International T2T Consortium
2023	Approved gene therapy for thalassemia and sickle cell anemia	FDA/EMA
2023	$300-400 human genome sequencing	Various companies
2023	Sequencing the genomes of Australian indigenous people	National Centre for Indigenous Genomics, Australia
2024	Gene editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) at the erythroid-specific enhancer region of BCL11A for sickle cell disease and β-thalassemia	Frangoul et al,; Locatelli et al.,

Figure 1.6 - *June 26, 2000 announcement of the completion of the first draft of the human genome sequence (from left: Craig Venter, Bill Clinton, and Francis Collins).*

do not involve changes in DNA structure) induced by the environment play a role no less important than constitutional genetic variations themselves in determining differences between individuals. The Human Genome Project and all related activities have not only greatly expanded our knowledge of disease genes but have also helped us understand the mechanisms by which mutations cause diseases, providing hints for the development of more effective therapies.

Since 1962, when Nobel Prize awarded Francis Crick, James Watson, and Maurice Wilkins, this foundation has dedicated about thirty prizes to genetic research. The path traced by this "revolution" promises an equally or perhaps even more innovative future. It is likely that the use of tools that, in the last twenty years, have reduced the time and cost of genomic analysis by over 200,000 times, will allow the development of "personalized medicine". Human DNA is destined to become a kind of medical record that we will be able to decipher to understand individual susceptibilities and resistances to diseases, and responses to drugs and to identify the most appropriate lifestyles. This new vision of medicine has several ethical, legal, and social implications that have not escaped the promoters of the Human Genome Project, who have allocated 5% of the total funds available to the study of these aspects.

Classification of Genetic Diseases

Hereditary diseases can be broadly classified into several main categories:

- Monogenic or Mendelian diseases: These are caused by mutations in a single gene (e.g., thalassemia, cystic fibrosis).
- Chromosomal diseases: These occur due to abnormalities in the number or structure of chromosomes (e.g., Down syndrome, Klinefelter syndrome).
- Multifactorial and Complex diseases: These arise from complex interactions between multiple genetic and environmental factors (e.g., heart disease, diabetes, cleft lip and palate, Alzheimer's disease, Parkinson's disease, and asthma).
- Mitochondrial diseases: These are caused by mutations in the mitochondrial DNA, which is inherited from the mother (e.g., Leber's hereditary optic neuropathy).

The prevalence estimates presented in Table 1.2 do not account for the recent findings from genome-wide association studies (GWAS), which have linked thousands of genetic variants to hundreds of common diseases, particularly in adults (e.g., cardiovascular diseases, inflammatory bowel disease). Additionally, the impact of somatic mutations, which can lead to cancer and other diseases, is not fully captured in these estimates.

Table 1.2 - *Approximate prevalence of genetic diseases in the general population.*

Type of genetic disease	Prevalence per 1,000 people over a lifetime
Autosomal dominant	3,0-9,5
Autosomal recessive	2,0-2,5
X-linked	0,5-2,0
Chromosomal	6,0-9,0
Congenital defect	20,0-50,0
Total	31,5-73,0

Figure 1.7 - *Medical geneticist V.A. McKusick (1921-2000), creator of the OMIM catalog of Mendelian traits.*

Mendelian Disorders

Archibald Garrod was the first to propose that not only alkaptonuria, but also albinism and cystinuria (a disease characterized by the inability of the proximal renal tubule to reabsorb cystine and other dibasic amino acids, leading to their precipitation in the urine as stones) were inherited in a recessive manner. In 1966, when Victor McKusick (Figure 1.7), the most authoritative medical geneticist in the United States during the second half of the 20th century, published the first edition of his famous "Mendelian Inheritance in Man" catalog, approximately 1,500 monogenic diseases and traits had been identified. By the 12th and final print edition in 1998, this number had risen to around 8,500. The online catalog (OMIM) contained, as of October 2024, over 27,500 entries (Table 1.3, Figure 1.8), of which over 26,000 were autosomal, over 1,370 were X-linked, 63 were Y-linked, and 72 were mitochondrial.

Table 1.3 - *Number of Entries in OMIM (Updated October 14th, 2024).*

MIM Number Prefix	Autosomal	X-linked	Y-linked	Mitochondrial	Total
Gene description	16,525	776	51	37	17,389
Gene and phenotype, combined	14	0	0	0	14
Phenotypes description, molecular basis know	6,478	388	5	34	6,905
Phenotypes descriptionor locus. molecular basis unknown	1,385	110	4	0	1,499
Other, mainly phenotypes with suspected mendelian basis	1,631	100	3	1	1,735
Total	26,033	1,374	63	72	27,542

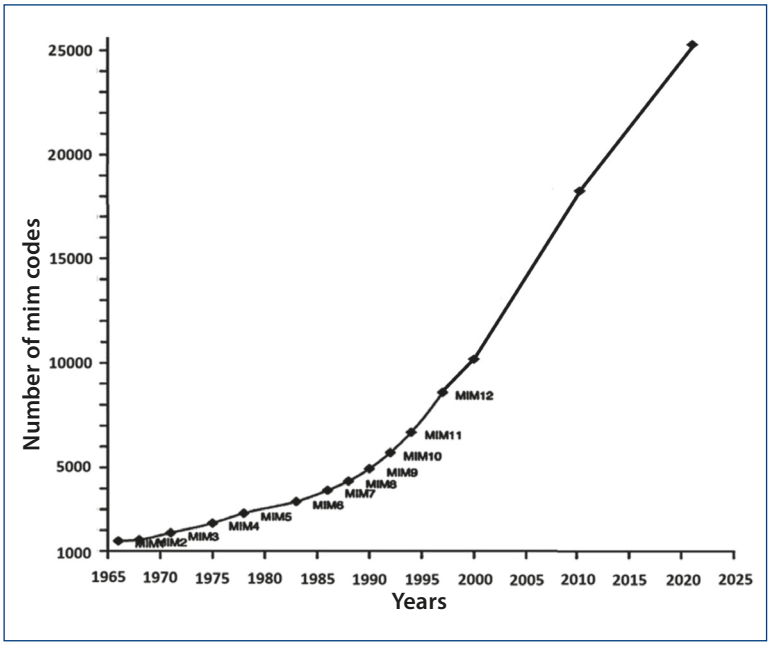

Figure 1.8 - *Progressive increase in the number of Mendelian phenotypes and genes between 1968 and 2021 in McKusick's catalog, in the paper editions (MIM 1-12), and in the subsequent online database.*

Chromosomal Disorders

A Dutch ophthalmologist, Petrus Johannes Waardenburg, was the first to propose in 1932 that Down syndrome (then referred to as "mongolism") might be linked to a specific abnormality in chromosomes. This hypothesis was confirmed in 1959 with the discovery of trisomy 21, marking the first identified chromosomal disorder in humans.

During the same period, major syndromes caused by an abnormal number of sex chromosomes were identified. For instance, monosomy X and the XXY sex complement were linked to Turner syndrome and Klinefelter syndrome.

In 1960, new syndromes associated with an abnormal number of non-sex chromosomes were described, such as trisomy 13 and trisomy 18. Additionally, researchers began to identify cases where part of a chromosome was missing (deletions), leading to conditions like chromosome 18 deletions and "cri du chat" syndrome (caused by a deletion on the short arm of chromosome 5).

A breakthrough occurred in the 1970s with the development of chromosome banding techniques. These techniques allowed scientists to visualize individual chromosomes and their specific regions, identifying numerous "new syndromes" caused by partial chromosomal imbalances.

Despite the introduction of techniques analyzing chromosomes at an early stage of cell division, when they are decondensed, and allow "high-resolution" studies with a definition up to five times greater than that obtained with traditional techniques, a substantial qualitative leap in the study of the karyotype occurred only from 1990 onwards, with the development of "molecular cytogenetics" techniques. These are protocols that combine chromosomal analysis and molecular biology, based on techniques, currently defined as FISH or Fluorescent In Situ Hybridization, in which DNA probes, labeled with fluorophores, bind to chromosomes or parts of chromosomes, allowing for specific identification with precision and resolution much higher than that of standard cytogenetics. The most recent evolution of cytogenetics has involved the development of so-called "virtual karyotypes", i.e., the ability to study the entire genome by analyzing changes in the copy number of bases. These investigations use arrays containing millions of copies of probes, onto which the DNA to be examined is placed. The genomic profile is reconstructed using sophisticated in silico software. This expression, literally "in silicon", is used to indicate chemical-biological phenomena reproduced in a mathematical simulation on a computer, rather than in a test tube (in vitro) or in a living organism (*in vivo*). Although the mathematical simulation has nothing to do with silicon, in fact, silicon is used in the construction of the electronic components of computers.

Multifactorial and Complex Diseases

Around the same time that Mendel was formulating his theories, Francis Galton (1822-1911), an eclectic explorer and anthropologist, the proponent of "eugenics", and a cousin of Charles Darwin, was studying complex and measurable traits, such as height and intelligence. Many of these studies utilized identical twins, in which differences are, by definition, attributable

to environmental influences. Galton introduced the "regression coefficient" into genetics to estimate the degree of similarity between different relatives. This concept was subsequently expanded, taking into account Mendel's discoveries, to try to understand whether certain characteristics, such as height and skin color, had a genetic basis, hypothesizing the interaction of multiple genes, each of which would have to act with a small additive effect. This was an innovative model, very different from that of monogenic diseases in which the mechanism, by definition, is not additive, as it concerns the main action of a single gene.

This model of quantitative inheritance has been widely accepted and has been used to explain the mechanism of transmission of many common diseases, which contribute significantly to the morbidity and mortality of the population (including various congenital defects and adult-onset diseases, such as diabetes, hypertension, stroke, and Alzheimer's disease). The current idea is that several genes, implicated in susceptibility, trigger the effect of some harmful environmental factors. This idea has been confirmed in recent years by thousands of genomic studies, which have allowed the identification of over 100,000 genetic variations associated with complex diseases and traits, which in recent years have been used to develop so-called Polygenic Risk Scores (PRS), which measure the effects and therefore the weight of genomic variations on the phenotype, or the susceptibility to develop a particular trait or disease.

Mitochondrial Diseases

Mitochondrial DNA is a circular structure containing a sequence of genes, inherited with the oocyte cytoplasm and therefore with maternal transmission. Only in the 1980s, a series of research studies, with Douglas Wallace and Salvatore di Mauro among the leading figures, led to the identification of the first diseases attributable to mutations in the mitochondrial genome.

These structures provide cells with energy in the form of ATP. Consequently, any congenital (present at birth) or acquired (during life) mechanism that can severely impair the production of ATP in the mitochondria can damage

or even kill cells, and cause a malfunction of tissues up to the appearance of clinical symptoms, when the number of mutated mitochondria reaches a "threshold" level. Some mitochondrial diseases are multisystemic, although the main target organs are the brain, eyes, and muscles.

The Spectrum of Human Diseases

The prevalence of some exemplary genetic diseases is reported in Table 1.4. While chromosomal and monogenic diseases are essentially dependent on hereditary characteristics, multifactorial diseases, as anticipated, originate from the interaction between genomic variations and the environment. These two categories differ from non-genetic diseases, which are essentially due to the action of environmental factors. A similar classification allows all human diseases to be included in a spectrum of continuous variability in which, proceeding from left to right, diseases of strictly genetic origin (G), those due to addition of genetic and environmental effects (G+A), and those due to environmental factors (A) are encountered (Figure 1.9). This model, therefore, establishes a gradient in which the hereditary component of the disease progressively decreases, proceeding from left to right. Nonetheless, some monogenic diseases are also largely influenced by the environment. The example of phenylketonuria, a metabolic defect that causes an accumulation of phenylalanine in the blood and secondary mental retardation, can be illustrative. If the newborn who has inherited the defect is fed with a low phenylalanine diet, he does not develop mental retardation, the most important clinical expression of the disease. On the other hand, some diseases attributable to the action of environmental factors can be significantly modified in their expression by the genetic characteristics of the individual. For example, the effects of a trauma, potentially at risk of causing a bone fracture, are more severe if the traumatized person has a genetically determined bone fragility (osteoporosis). Consequently, a person with osteogenesis imperfecta (a Mendelian disease associated with skeletal fragility), or osteoporosis (thinning of the bones), is more likely to experience a more significant clinical damage from a traumatic event than a person with intact bone structure.

Table 1.4 - *Approximate prevalence of some genetic diseases.*

Chromosomal Disorders	**Prevalence**
Down syndrome (trisomy 21)	1/1,800
Edwards syndrome (trisomy 18)	1/4,000-1/8,000
Patau syndrome (trisomy 13)	1/5,000-1/10,000
Klinefelter syndrome (XXY)	1/1,000 males
Turner syndrome	1/5,000-1/10,000 females
Monogenic Diseases	
Thalassemia	1/50-1/100 (Mediterranean and South Asia)
Hereditary non-polyposis colorectal cancer	Up to 1/200
Sickle cell anemia	Up to 1/50 in Central Africa 1/400-1/600 in African Americans
Familial hypercholesterolemia	1/500
Adult polycystic kidney disease	1/1,000
Fragile X syndrome (Martin-Bell syndrome)	1/5,000 males
Cystic fibrosis	1/2,500-4,000 Caucasians
Tay-Sachs disease	1/3,000 Ashkenazi Jews
Duchenne muscular dystrophy	1/3,500 males
Neurofibromatosis type 1	1/4,000-5,000
Hereditary hemochromatosis (symptomatic)	1/5,000
Osteogenesis imperfecta	1/5,000-1/10,000
Familial adenomatous polyposis	1/6,000
Myotonic dystrophy	1/8,000-1/10,000
Spinal muscular atrophy	1/10,000
Phenylketonuria	1/10,000
Hemophilia A	1/10,000 males
Marfan syndrome	1/10,000-1/20,000
Multifactorial Diseases	
Heart attack/stroke	1/3-1/5
Cancer (all types)	1:4
Diabetes (types I and II)	1/10
Alzheimer's disease (>65 years)	1/10
Alcoholism	1/10-1/20
Schizophrenia	1/100
Manic depressive psychosis	1/100-1/200
Congenital heart disease	1/100
Hypertrophic pyloric stenosis	1/300
Cleft lip/palate	1/1,000
Neural tube defects (in Italy)	1/1,000
Mitochondrial diseases	Rare

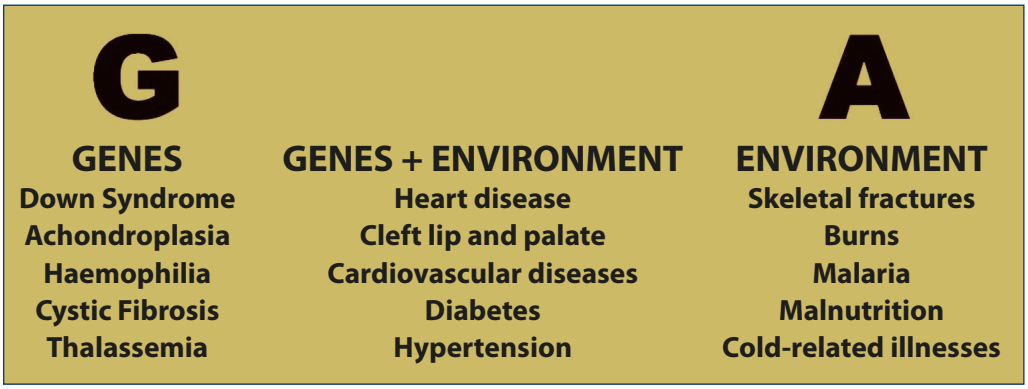

Figure 1.9 - *Spectrum of human diseases: proceeding from left to right, their genetic component progressively decreases. Some diseases, such as achondroplasia (a form of dwarfism) or haemophilia (a blood clotting disorder), are strongly conditioned by genes, while others (burns, traumatic diseases) are essentially due to the environment. Most common diseases fall in the middle part of the distribution and are due to the additive effect of genes and the environment.*

Impact of Genetics in Clinical Practice

Although genetics has produced results with a broad translational impact for several decades, genetic diseases are still perceived by many doctors as rare conditions that are only encountered exceptionally in the course of their professional careers. While it is true that there is a group of thousands genetic conditions whose individual frequency is less than 1:2000 (a criterion used in Europe to define a "rare disease"), considered as a whole, genetic diseases or those with a large genetic component are common enough to constitute a social-scale health problem. It is estimated that in Italy there are one-two million "rare disease" patients (80% of which have a genetic origin), and many millions of people suffering from common multifactorial diseases.

A century ago, health problems were by non-genetic diseases, such as malnutrition, diseases related to lack of hygiene, and infectious diseases, which were responsible for most childhood deaths. In the 20th century, the quality of public health improved significantly in industrialized countries, bringing genetic diseases to the fore as a significant cause of pediatric deaths (Table 1.5). Similarly, the percentage of hospitalizations in pediatric

Table 1.5 - *Percentage of pediatric deaths in UK hospitals attributable to non-genetic and genetic causes.*

Causes	London 1914	London 1954	Newcastle 1966	Edinburgh 1976
Non-genetic				
All causes	83,5	62,5	58,0	50,0
Genetic				
Mendelian	2,0	12,0	8,5	8,9
Chromosomal	-	-	2,5	2,9
Multifactorial	14,5	25,5	32,0	38,2

From Rimoin DL, Connor JM, Pyeritz RE, Korf BR: Emery and Rimoin's Principles and Practice of Medical Genetics, London, Churchill Livingstone, 2007.

divisions, attributable directly or indirectly to a genetic disease or a disease with a large genetic component, has increased and has been estimated at 27% in a study conducted in Seattle, 38% in a study in Mexico City, and even 71% in a 2004 study in the USA.

The amount of information available on medical genetics has increased significantly in recent years, facilitated, among other things, by the availability of high-quality, constantly updated online databases that allow real-time access to a vast amount of data. Clinicians and researchers can consult numerous databases and data banks free of charge, which allows them to be informed, for example, about Mendelian diseases and their respective disease genes (OMIM), rare diseases (Orphanet), genomic imbalances (DECIPHER), or other data on the human genome.

Although we are convinced that some traditional teaching tools will not become obsolete in the short term, certainly, only web-based electronic technology and the ability to navigate a vast array of multimedia content will guarantee, in the long term, adequate knowledge and dissemination of the results produced by genetic research.