全国高等学校教材 英文版

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医学遗传学

Textbook of Medical Genetics

主　编 Chief Editors
陈　竺 （Chen Zhu）

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主　编　陈　竺

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“英文版”出版说明

2001年8月，教育部制定并下发《关于加强高等学校本科教学工作提高教学质量的若干意见》（教高[2001]4号），指出：按照“教育面向现代化、面向世界、面向未来”的要求，为适应经济全球化和科技革命的挑战，本科教育要创造条件使用英语等外语进行公共课和专业课教学。对高新技术领域的生物技术、信息技术等专业，更要先行一步，力争三年内，外语教学课程达到所开课程的5%～10%。2005年1月，又印发了《关于进一步加强高等学校本科教学工作的若干意见》（教高〔2005〕1号），指出：高等学校要全面推广和使用大学英语教学改革的成果，要提高双语教学课程的质量，继续扩大双语教学课程的数量。要加强教材建设，确保高质量教材进课堂。

双语教育是提高学生英语水平的一个途径，尽管我国高等医学院校双语教学探索已有若干年，但教材的跟进始终显得滞后。没有合适的教材是目前双语教学面临的困难之一。2006年初，为推进双语教学的发展，经全国高等医药教材建设研究会和卫生部教材办公室审议，决定根据国家、地方和学生未来发展的需要，组织国内专家结合双语教学的经验，编写出版一套适应当前双语教学现状的教材。

此套教材的特点在于：

- 汇集名师。各教材主编均由卫生部规划的五年制、八年制教材的主编担任。
- 适合国情。教材的编写内容和体系主要参考我国医学院校长期使用并多次修订的五年制、八年制规划教材，更符合我国的教学模式。
- 语言纯正。根据引进的经典英文原版教材改编，聘请国外作者或编辑参与审校工作。
- 篇幅适中。由于双语教学的课时数有限，因此在编写时只选取各门学科需要重点掌握的内容（占中文教材内容的1/2～2/3）进行编写，也可减轻学生的负担。
- 丰富的教辅资源。教辅资源一直是外版教材的核心资源，因此，在本套教材编写的同时，我社引进了国外畅销的系列案例教材《Case Files》，以配合教学使用。
- 制作精美。为满足广大读者的阅读需要，全套教材采用双色印刷，图文并茂，版式清新美观。

本套教材共16种，全部为卫生部“十一五”规划教材。全套教材将于2007年秋季和2008年春季分两批出版发行。可供各医学院校针对五年制、七年制、八年制等不同层次学生开展双语教学使用。

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Contents

Chapter 1 Genetics in Medicine

GENETIC BASIS OF HEALTH AND DISEASES

All living organisms, including human beings, obtain energy and maintain biological activities through material exchanges with the environment. With the help of our metabolism, nutrients and other materials from the surrounding world are absorbed and subsequently transformed into useful building blocks of the body whereas waste metabolites are excreted from the organism. It has been well established that the metabolic pattern is largely determined by an individual's genetic background of the species as a result of evolution. Hence, the health of human being depends on a balance of the genetically regulated metabolism and the changing environmental conditions. Defects in genetic information embedded in the deoxyribonucleic acid (DNA) sequence of the genome and/or profound changes of the environment disrupt this balance and lead to diseases. Analysis of the human disease spectrum reveals an interesting phenomenon: the weight of the genetic and environmental factors varies significantly according to the etiology of different diseases. For example, trauma, intoxication and nutritional diseases are primarily caused by environmental factors. In contrast, diseases like galactosemia and phenylketonuria (PKU) are due to gene mutations or Down syndrome and Turner syndrome caused by constitutive chromosomal abnormalities which are mainly genetic in nature and can occur only in patients who carry these mutations or chromosomal aberrations. However, most diseases should be placed between these two extremities and result from a combination of both factors. Therefore, common diseases such as cancer, cardiovascular diseases, diabetes, rheumatoid arthritis and peptic ulcers have genetic predisposition reflected by the numerous affected members in the same family, although the onset of diseases is often triggered by certain environmental challenges. It has been proposed that the genetic factors in these common disorders are produced by accumulation of relatively small effects of many genes. It is also interesting to note that some hereditary diseases with well defined genetic defects need environmental triggers to trigger their clinical manifestations. One typical example of these is a variant of the glucose-6-phosphate dehydrogenase (G6PD) deficiency in which the crisis of hemolysis comes only after exposure to fava bean, anti-malaria agent primaquine or other oxidants. Conversely, it is now generally accepted that genetic factors can play a major role in the susceptibility or resistance to viral or bacterial infections, diseases previously thought to be "non-genetic", as well as in the immune response to infectious agents.

Over the past half century, with the tremendous development of socio-economic conditions, a

marked reduction in nutritional and infectious diseases has been achieved in many countries, particularly the developed ones, and it has promoted the awareness of the role that genetics play in human health and disease. According to a report of World Health Organization (WHO) in 1971, among 1,146 hospitalized patients in the Montreal Children's Hospital of Canada, diseases related to gene defects including genetic and multi-factorial diseases accounted for 29.4%. The incidence of genetically related diseases has been experiencing a major change in the urban population of China. For example, in Beijing, congenital heart disease accounted for only 2.6% of all infant mortalities in 1951, whereas the figure increased to 30% during 1974 to 1976, ranking the second highest cause of infant death. Congenital abnormalities such as mental retardation and congenital gastrointestinal malformation were, as a group, the first killer of children under 15 years old during 1974 to 1976. On the other hand, there has been considerable increment of life expectancy in China over the past 5 decades, which was accompanied by a big change in disease spectrum of the percentages of genetically related diseases such as cancer and chronic diseases increasing in all age groups.

It is worth pointing out that the incidence of genetic diseases can be different among distinct populations. For example, β-thalassemia, a disease of hemolytic anemia with reduced level of β-chain of hemoglobin (Hb), is the most common form of thalassemia in Mediterranean countries; while in East Asian populations, α-thalassemia characterized by reduced synthesis of α-chain of Hb, is the dominant form of thalassemia. Cystic fibrosis, a genetic disease leading to pulmonary dysfunction, has a rather high frequency in Caucasian population (1 out of 2,000) whereas it is extremely rare in Chinese population. Whether the unusual expansion of some of these disease alleles in certain populations might reflect a "shaping" of the genetic information as a mechanism of adaptation to the environmental pressure through the evolution needs further study.

BRIEF HISTORY OF MEDICAL GENETICS

Early Knowledge about Hereditary Diseases

The initial concept of genetics could be traced back to the period of Hippocrates of the ancient Greece, when some diseases were recognized to be transmissible through family lineage. About 1,500 years ago, the Hebraism Code had already rules forbidding the circumcision for male members of families with bleeding tendency, representing the early awareness of the genetic inheritance of hemophilia. In the 18th century, Maupertuis described families with polydactyly and those with defects in skin and hair pigmentation (albinism), pointing out two distinct patterns of hereditary diseases. In 1859, Baedeker made the diagnosis of alkaptonuria as the first recognized inherited metabolic disease.

The founder of modern genetics was Mendel (1822—1884), an Austrian clergy. In his famous article on hybrid bean experiment, published in 1866, he described that hybrid breeding of yellow bean and green bean produceed yellow F1 bean. He then suggested that the yellow colored beans had a genetic trait dominating the green ones. However, when auto-pollination was allowed, two-colored beans were observed in the offspring. Hence, Mendel reasoned that the inheritable traits should be determined by paired genetic factors. When reproductive cells (gametes) were formed, these paired factors are separated and respectively entered into two

gametes. This reasoning was later called as the first law of Mendel, or law of segregation. At the meantime, Mendel believed that in the course of zygote formation, these distinct genetic factors should be recombined freely. This was later called Mendel's second law, or the law of independent assortment. These two laws, which were both confirmed by numerous experiments many years later, constitute the central part of Mendel's theory of genetics. However, Mendel's work didn't arouse sufficient attention when he was alive and was only re-discovered in 1900. This re-discovery immediately prompted application of Mendel's theory into human genetics. Farabee pointed out that the brachydactyly was a dominant trait in 1903, which was recognized as the first example of autosomal dominant trait. In 1901, Garrod described 11 patients from four families with alkaptonuria. As noted, the parents of three patients were second brothers and sisters and presented with normal phenotype. Bateson, a geneticist of that time, reminded Garrod that alkaptonuria was a disease of autosomal recessive inheritance. Since these patients had the same maternal grand parents, they shared the same genetic factors. The consanguineous marriage should then allow the genetic factors from both parents to be transmitted to the offsprings.

Later on, many genetically related human traits were found coincide with Mendel's law. However, there was also a tendency to generalize this concept to human diseases in an oversimplified approach. This was problematic because many diseases are multi-factorial and these diseases, although with genetic susceptibility, don't follow the typical model of Mendelian inheritance.

An important observation was made by Sutton and Boveri in 1903. They noticed that the behavior of genetic factors was in parallel to that of chromosomes. Based on this observation, they proposed that the genetic factors should be located on chromosomes. This was where the theory of chromosome genetics was originated. In 1909, Johannsen renamed the genetic factors as "gene".

Before 1905, most of the genetic manipulations were performed in plants. In 1905, Castle used drosophila (fruit fly) as a model organism to carry out genetic experiments. The drosophila is a species relatively easy to be raised and maintained since fruit flies are capable of producing 20~25 generations a year. In addition, drosophila has only 4 pairs of chromosome and therefore represents a simple system to conduct analysis. Around 1910, Morgan and his students Sturtevant, Bridges and Muller from Columbia University in USA, started to look at the hereditary patterns of traits in drosophila. They found that all traits could be divided into 4 linkage groups, corresponding to the number of chromosomes. They deduced that chromosomes could be the transmission units of the heredity factors. Hence, linked genes on one chromosome can be transmitted as one unit to the offsprings. This is the law of linkage. Nonetheless, the linkage is not absolute in that during the gametogenesis there are exchanges of fragments of genetic material between homologous chromatids, creating a re-assortment of genes in the new linkage. This is known as the law of crossing-over.

Johannsen was not only the first person to use the word "gene", but also the founder of the "genotype" and "phenotype" concepts. The genotype concept denotes the genetic structure of an individual and the phenotype concept stands for the traits presented by an individual as a result of the interaction between the environmental conditions and the genotype. However, with regard to human genetics, it was as early as 1875 that Galton had already distinguished the influences of the genetically transmitted traits (nature) from the acquired ones (nurture). Galton believed that identical twins shared the same

genetic structure and therefore the same genotype. However, distinct phenotypes might appear if the twins grew in different environments. Galton was very interested in the genetics of human physique and intelligence. He introduced the statistical concept of regression coefficient to the study of genetics in order to estimate the similarity among family relatives. His work laid a solid foundation for the study of mathematic issues in human genetics. Galton also raised a concept to improve the genetic constitution of human being and animals and designated it "eugenics". Unfortunately, the mis-use and dissimilation of the concept of eugenics lead to the "eugenics movement" of anti-science and anti-humanity under Hitler from 1930s to 1940s.

Adams was also a man with great reputation in the early development of medical genetics. In 1914, he published a paper to discuss the differences among congenital diseases, familial and genetic diseases. He shed insights into the relationship between genetic diseases and age of the onset of the disease, environmental factors and consanguineous marriage. He touched on a number of essential aspects concerning genetics. He deduced a number of fundamental principles of the heredity factors in a quite logical manner.

Emerging of Medical Genetics

Medical genetics is a relatively new discipline as a result of mutual infiltration of clinical medicine and genetics. It is an integrated part of human genetics. Since 1950s, medical genetics has made very rapid progress due to the development of biochemistry, cytogenetics, immunology and the inter-disciplinary researches among them, as well as the advancement of a great number of innovative experimental techniques of molecular genetics.

As aforementioned, when Garrod investigated alkaptonuria, he wisely deduced that alkapton should be the degradation product of tyrosine. He further reasoned that because of the congenital enzyme deficiency, alkapton couldn't be oxidized and therefore accumulated in the body and excreted in the urine. In 1958, La Du and his colleagues confirmed the hypothesis of Garrod by showing the absence of the alkapton oxidase in the liver tissue biopsy of the patients. Now, a vast array of metabolic diseases caused by genetic enzyme deficiency has been described. Since 1950s, with the innovation of experimental techniques and analytical tools in biochemistry, the level of research and clinical diagnosis of congenital metabolic diseases has been dramatically heightened. For example, chromatography can easily detect the abnormal metabolites in urine; electrophoresis technique allows rapid and reliable detection of abnormal Hbs; starch gel electrophoresis permits characterization of the structural abnormalities of proteins including different enzymes. In short, technological development has been significantly promoting medical genetics from both theoretical and practical perspectives.

Theoretically, the most impressive progress has been achieved in the research on Hbs. In 1949, Pauling studied sickle cell anemia and identified an abnormal Hb molecule HbS with an electrophoresis behavior being different from that of the normal HbA. The concept of "molecular disease" was raised for the first time. Then Ingram invented the protein "finger printing" method and discovered that a glutamic acid located at the amino acid position 6 of HbSβ was replaced by valine, which greatly stimulated the study on the hemoglobinopathy as a molecular disease.

In practice, different approaches in the treatment of certain genetic diseases were proposed in 1950s and one significant breakthrough was the therapy of PKU. Bickel and his colleagues reported that restriction of phenylalanine intake among infants with PKU could prevent the disease and might

also give rise to therapeutic effects. This work greatly promoted the early detection of genetic diseases as well as the research on methods for the prevention, control and treatment of hereditary metabolic diseases.

In the mid-1950s, a genetic trait with hypersensitivity to acetyl-choline was found to be caused by deficiency of the serum acetyl-choline esterase. Meanwhile, the hemolytic anemia after exposure to primazine was found to be associated with the deficiency of G6PD. These discoveries proved that there should be a genetic basis for drug metabolism. In 1959, Vogel proposed the concept of "pharmacogenetics", which was further developed in 1970s. The genetic basis should be taken into consideration not only to understand the individual differences in drug responses, but also to identify those in responses to all environmental factors. In 1971, Brewer proposed the term "ecogenetics" to strengthen the importance of genetic background in determining the responses to drug, medication and toxins in the environment.

Development of Cytogenetics

In 1956, J. H.Tjio and Levan performed careful scrutiny of human fetal lung tissue culture and pointed out, for the first time, that the exact number of human chromosomes in somatic cells should be 46. In the same year, Ford and Hamerton observed the chromosomes at the metaphase of the human spermatoblasts and confirmed this discovery. However, the widespread use of chromosome analysis method should be ascribed to the discovery made by Hsu in 1952 when he found the low osmotic treatment could make the swelling of the cells so that the chromosomes could be spread out for clear observation. In 1956, Tjio used colchicine to block the entrance of the cells into anaphase, resulting in an increased number of metaphase in cell culture. In 1960, Nowell used phytohemagglutinin (PHA) to stimulate *in vitro* the cultured human lymphocytes to enter into cell division. In the same year, Moorhead and his colleagues combined the *in vitro* culture of human lymphocytes with chromosome preparation to form a simple but reliable working system for karyotyping. This technique was immediately used in clinical after characterization of an exact number of human chromosomes. In 1959, a series of major discoveries were made: Lejeune and his colleagues discovered the trisomy 21 in Down syndrome, *i.e.*, an additional chromosome 21, a small chromosome with acrometric appearance; Ford found the lack of one X chromosome in women with Turner syndrome; Jacobs and Strong discovered that men with Klinefelter syndrome were characterized by a karyotype of 47, XXY. In 1960, a group from Philadelphia discovered a non-random chromosomal marker, the Philadelphia chromosome (Ph^1) in leukemia cells from patients with chronic myelogenous leukemia (CML). Later on, a number of clinical syndromes with chromosomal abnormalities or marker chromosomes in cancer were reported. In the end of 1960s, Caspersson and his colleagues discovered that, when stained with a fluorescent colorant of quinacrine mustard, distinct bands could be observed on each of the chromosomes of the plant mitotic cells. The accuracy of chromosome analysis was then significantly increased and a large number of chromosomal anomaly-related syndromes were thereafter identified.

Development of Immunogenetics

The application of experimental techniques in immunological disease studies enlarged the concept of inherited disorders and brought new methods in disease control and prevention. In 1900, Landsteiner discovered the ABO blood

group antigen system. In the first half of the 20th century, a dozen of blood group antigen systems were discovered using red blood cell (RBC) hemagglutination test, laying the basis for blood transfusion. Levine and his colleagues made a hypothesis in 1941 that the fetal erythrocytolysis (fetal hemolytic anemia) could result from the alloimmunization due to the incompatibility of the RBC blood group antigens between mother and fetus. In 1952, Dausset and Nenna discovered a white blood cell (WBC) hemaglutinin among patients after multiple transfusions. In 1958, the first human leucocyte antigen (HLA) Mac (HLA-A2+A28) was discovered. In 1964, Terasaki and McClelland designed the micro-lymphocyte-toxicity test to replace the WBC hemagglutination test. Using this new immunogenetic technique, the HLA system was discovered as a highly polymorphic system of human being. This breakthrough made the tissue typing of the donors and recipients in organ transplantation possible. Moreover, in 1950, Glanzmann and Rinicker described the severe combined immunodeficiency (SCID) as an inherited clinical syndrome. In 1952, Bruton reported the hypogammaglobinemia and humoral immunodeficiency. Nowadays, a series of genetically immunodeficient diseases with distinct transmission patterns and various clinical manifestations have been reported.

Development of DNA Based Molecular Genetics

In 1970s, with the discovery of the restriction endonuclease and the establishment of DNA hybridization technology, molecular genetics entered a new era of genetic engineering and provided unprecedented means to solve clinical problems. Y. W. Kan and his colleagues (1976), Wong and his colleagues (1978), and Dozy and his colleagues (1979) made the first prenatal diagnosis of the α-thalassemia through applying DNA technology to the sample of fetal amniotic cells. Owing to the strict nucleic acid sequence specificity of the restriction enzymes in digesting DNA, in the case where DNA sequence of an individual is changed by genetic variation, the normal restriction site may disappear while new restriction site may appear. Hence, the DNA fragments digested with restriction enzymes may show different patterns in the population. By using this restriction fragment length polymorphism (RFLP) in the population and the linkage between certain RFLP patterns and disease loci, Y. W. Kan and his colleagues (1978) made the first prenatal diagnosis of sickle cell anemia in the DNA of fetal amniotic cells. Over the past three decades, this method was used for diagnosis at DNA level of many genetic disorders such as PKU and hemophilia A.

Taking the progress of the medical genetics since 1950s as a whole, the study on the biological variations in disease pathogenesis shifted gradually from the description of phenotypes to the variation of proteins and then to the variation of DNA structure. In the mid 1970s, molecular genetics allowed the discovery of the oncogenes and tumor suppressor genes. This discovery paved the way to the concept that somatic mutations constituted the molecular basis of most human cancers. Somatic mutations may also be the molecular basis of many auto-immune diseases and the process of aging.

In 1990, gene therapy as a new movement in medical genetics started its first clinical trial. Gene therapy denotes the transfer of a normal gene into the somatic cells of a patient. Expression of the transferred gene could then provide the normal protein products deficient in the patient so that therapeutic effects could be attained. The first trial of gene therapy was carried out for the SCID with a deficiency of adenosine deaminase (ADA) and hemophilia B with a deficiency of coagulation

factor IX. Though certain effects were reported in these preliminary trials, a real breakthrough was made by Fisher's group in Paris in 2000 in the gene therapy of a different form of SCID. However, the bio-safety issue of gene therapy as well as the question of how to regulate the expression of transferred gene remains the major concerns.

A big difference realized due to the progress of the molecular genetics is the new concept of reverse genetics. In contrast to the classical way of doing genetic analysis from the phenotype to the protein and then to the genotype, reverse genetics first seeks the mapping of the disease loci on the human chromosomes by pedigree linkage analysis using the polymorphic DNA markers and then detects the mutations of DNA sequences responsible the disease, even without knowing the abnormality at the protein level. Once the disease gene is identified and the disease-causing DNA variation is detected, the primary protein structure and corresponding amino acid sequence abnormalities can be deduced. Hence, this approach is one that starts from the genotype analysis and then extends to the analysis at protein and phenotype levels. Over the past two decades, guided by reverse genetics, geneticists carried out linkage analysis with polymorphic DNA markers to study a great number of genetic diseases, and cloned the disease-causing genes, including those responsible for very important genetic disorders such as the dystrophin gene involved in Duchenne muscular dystrophy, and cystic fibrosis transmembrane regulator (CFTR), a chloride transporter of which the mutations were responsible for CF.

Molecular biology has led medical genetics to a completely new dimension at the turning point of the 21st century. The Nobel laureate Dulbecco commented in 1986 in a famous paper named "*A Turning Point in Cancer Research: Sequencing the Human Genome*", and said "*If we wish to learn more about cancer, we must now concentrate on the cellular genome...I think that it will be far more useful to begin by sequencing the cellular genome. ...In which species should this effort be made? If we wish to understand human cancer, it should be made in humans because the genetic control of cancer seems to be different in different species. Research on human cancer would receive a major boost from the detailed knowledge of DNA*". After several years of debate within the academia, the US parliaments established a 15-year plan to support the Human Genome Project (HGP) with a budget of 3 billion USD. Three steps were defined in this plan: first, to establish a linkage map (or genetic map), second, to have a physical map, and third, to get the 3×10^9 bp human genomic DNA sequenced. HGP has been considered as the Apollo Project in the history of biomedical science and has been expected to bring a new boost on the genetics and possibly in biomedical science as a whole. In view of its huge and profound impact, HGP aroused a lot of attention from the governments and industries of many countries which increased the investment from different sectors from the initial estimated funding and facilitated the research progress to stay ahead of schedule. On June 26th, 2000, Bill Clinton, the acting President of USA and Tony Blair, the acting Premier of UK at that time, declared that the HGP had been accomplished to obtain the draft sequence of human genome. On February 15th, 2001, the International Human Genome Sequencing Consortium (IHGSC), supported by the governments of USA, UK, Japan, France, Germany and China, published the results of the initial analysis of the draft sequence of human genome in Nature, whereas one day later, the result of draft sequence generated by a private company Celera was published in Science. On October 21st, 2004, Nature published the

Table 1-1 Major events in molecular medical genetics

Year	Event	Main author(s)
1860	First isolation of DNA	Miescher
1944	Evidence for DNA, but not protein, to be the carrier of genetic information during the bacterial transformation	Avery
1953	Discovery of DNA double helix structure	Watson, Crick
1961	Evidence of denaturation of DNA, which laid the foundation for the specificity and feasibility of nucleic acid hybridization	Marmur, Dory
1962	Discovery of DNA restriction endonuclease	Arber
1966	Demonstration of DNA genetic codon	Nirenberg, Ochon, Khorana
1967	Discovery of DNA ligase	Gellert
1970	First synthesis of gene in the test tube	Khorana
1972-1973	DNA recombination technology	Boyer, Cohen, Berg
1975	Detection of specific DNA sequence using gel transfer and hybridization	Southern
1975-1977	Rapid DNA sequencing	Sanger & Barrel, Maxam & Gilbert
1977	First cloning of human gene	Shine
1978	First application of RFLP	Kan
1978	First DNA diagnosis	Kan
1981	Sequencing of the first human mitochondrion	Anderson
1985	First demonstration of DNA "finger printing"	Jeffreys
1985	Invention of the polymerase chain reaction (PCR)	Mullis, Saiki, Erlich
1986	Proposal for sequencing of human genome to solve the genetic basis of human cancer	Dulbecco
1990	First clinical gene therapy for adenosine deaminase (ADA)	Anderson
1991	Launch of 15-year plan of HGP	Watson, Collins
1994	Genetic map of human genome	Murray, Weissenbech, White, Ward, Dausset
1998	Physical map of human genome	Delonka, Schuler, Gyapay, Beasley
2001	Annotation of the human genome based on draft sequence of 94% of human genomic sequence	IHGSC, Celera
2004	Completed human genome sequence covering 99% of euchromatic region with an error rate of less than 10^5	IHGSC

completed high quality sequences of the human genome by IHGSC (Table 1-1). This great event in the history of human molecular genetics will certainly direct the progress of the biomedical science in the 21st century, of which the knowledge and technological innovations must bring major benefits to human society.

Up to now, medical genetics has become a discipline of science which connects both basic and clinical researches with a number of branches (Table 1-2).

Table 1-2 Branches of medical genetics

Cytogenetics	Somatic cell genetics
Biochemical genetics	Cancer genetics
Molecular genetics	Population genetics
Pharmacogenetics	Genetic epidemiology
Immunogenetics	Clinical genetics
Behavior genetics	Genomics
Ecogenetics	Pharmacogenomics
Radiation genetics	

CLASSIFICATION OF GENETIC DISEASES

Genetic diseases are generally divided into five categories. While analyzing the genetic basis of clinical disorders, it is essential to determine which category the disease settings belong to.

Diseases Caused By Chromosomal Abnormalities

Normal human somatic cells are diploid cells and therefore have two sets of 23 chromosomes (46 in total). If errors occur at the time of the gamete formation or at the very beginning of the early life of an embryo, the affected individuals may have an abnormality in the number of chromosome, either more or less than usual. This abnormality may be at the level of an entire chromosome or at the level of a segment of chromosome and the affected individuals will have a variety of congenital defects in the development stage. For example, there is a trisomy 21 (the presence of an extra chromosome 21) in Down syndrome. Usually, chromosomal disorders are not transmitted in the families, except for a few cases. There are over 300 known chromosomal disorders. The chromosomal disorders have an incidence of 0.7% at birth whereas they may be responsible for about half of the spontaneous abortion cases in the first trimester of pregnancy.

Single-Gene Disorders

Single-gene (or monogenic) disorders result from the mutation of genes. On the pair of the homologous chromosomes, the mutation could occur on just one allele or on both. Usually, single-gene disorders exhibit characteristic patterns of transmission in the pedigree. Although most individual single-gene disorders are not frequent, with an maximum of 0.2%, due to their great variety and increasing recognition number, the sum of these disorders is quite remarkable [8,587 in the 12th edition of *Mammalian Inheritance in Man* (MIM)].

Polygenic Disorders

Polygenic disorders are also called complex trait diseases. These diseases are derived from the combination of both genetic background and environmental factors, and include a number of congenital developmental defects and particularly a variety of common diseases. There is a tendency of familiar aggregation in these diseases, but no clear pattern of family transmission is observed.

Genetic Diseases of Mitochondria (Mt)

Mitochondrial DNA encodes a part of proteins involved in respiratory chain of Mt. Moreover, rRNAs and tRNAs for protein synthesis within Mt are also encoded by Mt DNA. Mutation of Mt genes may cause Mt genetic disorders and the transmission of these diseases is in parallel to the transmission of Mt (or cytoplasmic transmission) and is, as a result, in concordance with the maternal heredity in most cases.

Somatic cell disorders

It is well known that cancer is caused by mutations in genetic material and some families may show genetic susceptibility to cancer. However, the tumor foci of the somatic cells display clonality and their formations result directly from the mutations of genetic materials of somatic cells. Hence, most cancers belong to somatic cell genetic disorders and some congenital disorders also belong to this kind.

It is not always easy to determine if a disease is of genetic origin. The infectious diseases might even have a genetic predisposition. The following clues may suggest a genetic etiology in human

diseases:

1. The patient has characteristic phenotype (usually accompanied with mental retardation) and chromosomal abnormality, with or without family history of the same disease or related disorder;

2. In the absence of environmental factors, the same disease manifestations are found in a certain proportion of the relatives of the index case;

3. Absence of the specific disorders in the non-consanguineous family members (such as spouse);

4. In the absence of known triggering factors, the patient has quite unique age of disease onset and disease course;

5. The frequency of having the same disease is significantly higher in identical twins than in the non-identical twins.

TASKS AND PERSPECTIVES OF MEDICAL GENETICS AND GENETIC MEDICINE

The mission of medical genetics is to uncover the basic laws and pathogenesis of various forms of genetic diseases and thereby build up the foundation for appropriate diagnostic and preventive measures. Genetic medicine, on the other hand, provides clinical services, including diagnosis, treatment, screening, prevention, counseling and follow-up consultations to patients with genetic diseases. The ultimate goal aims to relieving the suffering of the patients so that they can also enjoy their lives. Since 1978, major medical centers in big cities of China have gradually been establishing outpatient departments for pre-marriage examinations and genetic counseling in conjunction with the family planning program. The genetic medical service in different clinical specialties has also been drawing a lot of attention. Overall, genetic medicine will make a substantial contribution to the modernization of medicine in our country.

According to the annotation of the finished DNA sequence of human genome by IHGSC, there are about 25,000 protein-coding genes in the human genome, accounting for 1.1%~1.4% of the entire human genomic sequence. However, it has been found that human genome possesses a huge quantity of single nucleotide polymorphism (SNP), about $(3\sim10)\times10^6$ in number, which was revealed over the course of the HGP. The approach of positional cloning in identifying disease genes has been largely facilitated by HGP. It can be speculated that all genes responsible for single-gene diseases will be ultimately discovered. In the new century, the emphasis of medical genetics study will be moved to the study on multi-factorial disorder and cancer. These complex trait diseases involve a close interaction between numerous genetic components and extremely complicated environmental factors. Indeed, SNPs can offer invaluable polymorphic biomarkers for the investigation of both multi-factorial disorders and different types of cancer. To fulfill this task, the regulatory mechanisms at the genomic level must be addressed.

In the functional genomics era, the development of medicine requires a thorough characterization of the comprehensive information of the genetics, epigenetics (regulation of gene expression without changes in DNA sequences) and environment under both physiologic and pathologic conditions. The discovery of protein-coding genes is fundamental to the mass production of protein products by using transgenic plant or animal bioreactors. The emphasis of the analysis of genome has been shifted from the structure to the function, and more recently to the proteome and metabolome. Understanding of the biological meanings of the non-coding sequences, which represent a large majority of the genomic