Medical Genomics and Genetics

Achievement

Establishment of medical genetics and contributions to its development

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OUTLINE:

With the completion of the human genome project, we have come to understand almost all of the genetic information contained in DNA, which is encoded in a series of letters. However, we are still some way from fully identifying those parts which are related to the treatment of diseases. Dr. Victor A. McKusick, recipient of the current fiscal year's Japan Prize in the category of "Medical Genomics and Genetic", has spent over half a century compiling related knowledge, and advocating the importance of the formulation of a genomic map for genetic disorders. Today, researchers and clinicians around the world are sharing the fruits of Dr. McKusick's labors which have become indispensable to the world of genetic medicine.

In the Human Genome Project, which commenced in 1990 and was completed in 2003, the DNA sequence of every single chromosome was determined. Within the determined genomic information, it was discovered that there are in vivo parts that perform vital functions. However, there are also parts of which the function is unclear, and these parts remain merely an undetermined series of letters. From among this seemingly meaningless series of letters, it is important to identify the parts with genetic functions, decode the series of letters and thus clarify the function of the protein. Understanding the relationship between genomic function and genetic diseases is vital to accurate interpretation of the human genome. Dr. Victor A. McKusick has spent over half a century investigating which DNA sequences of which DNA loci cause genetic disorders, and has been steadily compiling related information.

From cardiovascular diseases to genetic medicine

Dr. McKusick was born in 1921 into a dairy farming family in a town with a population of approximately 500 residents in the northeastern US state of Maine. In 1943, he was accepted to the Johns Hopkins University, famous for its medical research, where he studied medicine. Specializing in heart-related diseases, Dr. McKusick became interested in Marfan syndrome, a genetic disorder that causes cardiovascular abnormalities. Later he established a field of medical study, known as medical genetics to study the genetic causes, treatments and prevention of inherited diseases, and feverishly set about a genetic mapping (chromosome mapping) project.

Laying the foundations for genetic medicine

Marfan syndrome is a genetic disorder of the connective tissue which maintains the shape of the body (e.g. gaps between cells, cartilages, etc.), and is characterized by disproportionately long limbs and fingers. It also affects the heart and cardiovascular valves and vessels, as well as the eyes. It had been known for some time that this was a genetic disease, but as patients were affected in different parts of the body it was not thought to be related to the mutation of a single gene. However, through analyses of vast amounts of data related to Marfan syndrome, Dr. McKusick and his research team at the Johns Hopkins University identified Marfan syndrome as a condition caused by the mutation of a single gene.

In 1956, Dr. McKusick published *Heritable Disorders of Connective Tissues*. Through his clinical experience of patient examination, he realized the importance of identifying the roles of genes in human diseases, and in 1957 he set up the world's first Division of Medical Genetics, a new branch of clinical medicine at the Johns Hopkins University. Today, this research center has been designated the McKusick-Nathans Institute of Genetic Medicine in commemoration of the achievements of Dr. McKusick. It was here that he devoted his energies to researching various genetic diseases besides Marfan syndrome, and where he became the first person to clarify the genetic role in several diseases including cartilage-hair hypoplasia and McKusick-Kaufmann syndrome.

In 1968, a research team he was leading identified a gene that determines the assignment of a blood type, known as the Duffy blood group locus, or Duffy antigen system, to chromosome 1. This was a landmark discovery that identified the exact location of the specific gene in autosomes, excluding the sex chromosomes, and this led to the world's first attempt at a genetic map. A genetic map gives a detailed depiction of which genes exist on which chromosomes, and on which exact part of each particular chromosome they are located. At the time, the mapping project required a massive amount of research on family lineage and hereditary diseases, and close observations of chromosomes. It was indeed a project on a grand scale that necessitated both a great deal of experience and instinct.

The creation of a comprehensive database of genetic diseases

In 1969, Dr. McKusick proposed that the utmost efforts be exerted to identifying the genetic sequence of human chromosomes at the International Conference on Congenital Disease where he reported on his discovery of the Duffy antigen system.

In 1973, Dr. McKusick's team led a Human Gene Mapping Workshop which included several other research groups. The aims of the workshop included information exchanges and the formulation of a system for consistent genetic designation. This workshop later developed into the Human Genome Organization (HUGO).

Dr. McKusick's greatest achievement was his publication of the reference work *Mendelian Inheritance in Man*. First published in 1966, 12 editions of this reference work were printed until 1998, and constitute a comprehensive cataloging of the relations between human genes and genetic disorders.

In 1987, an online version of *Mendelian Inheritance in Man* (OMIM) was opened to the public. This online version obtains the latest research data before it is published in scientific journals, and allows researchers and clinicians around the world to access the very latest available information. It is even said that there is no genetic clinician in the world today who has not referred to *Mendelian Inheritance in Man* at some point. Undaunted by the perseverance and endurance necessary for the collecting of such a huge amount of data, Dr. McKusick set about the creation of a framework for the systematic collection of data.

Leading the Human Genome Project

Dr. McKusick also worked assiduously toward the foundation of the Human Genome Organization (HUGO), a development of the aforementioned Human Genome Mapping Workshop, in order to bring together researchers on the Human Genome Project to exchange information and to coordinate operations. Dr. McKusick himself served as the first president of the organization. From the production of the very first genetic mapping prototypes through to today's genomic map that is able to determine the entire human genome sequence, Dr. McKusick has been an instrumental figure, constantly playing a leading role in international genetic research.

Dr. McKusick is a man of remarkable foresight. As long as over half a century ago, he strongly advocated giving full recognition to the critical roles played by genes, and this has resulted in the compilation of a vast amount of genetic data that, given the technological innovations in recent years, continues to increase in importance. Dr. McKusick has been instrumental in the establishment of a new field of medical study which is able to utilize genetic data and ascertain the role of genetics in a variety of disorders, and even enables personalized medicine for patients suffering from cancer or diabetes through the ability to determine the slight genetic differences of each individual.

Dr. McKusick has published some 760 academic papers, and his extensive output is further testament to his boundless human compassion and dedication to eradicating genetic disorders in children. Even today, he continues to stand at the forefront of the latest developments in clinical genetics, and the immense respect with which he is accorded around the world makes Dr. McKusick an extremely worthy recipient of the Japan Prize.