Molecular Genetics and Genomics in Medicine

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Siriraj Med J 2008;60:270-272
E-journal: http://www.sirirajmedj.com

In the past few decades, a remarkable progression occurred in the field of Human Genetics – the discipline that provides essential knowledge to understand human biology in normal and abnormal conditions. This was importantly attributable to the strong impetus of the Human Genome Project (HGP), the internationally collaborative effort to sequence the whole human genome comprising about 3.2 gigabases (Gb) and to identify about 25,000 human genes. This project announced its success on April 14th, 2003[1] – two years ahead its original schedule which was coincidentally the 50th anniversary of Watson and Crick's discovery of the double helical structure of DNA[2].

Since the HGP produced enormous data of human and model-organism genomes, during the project '**Bioinformatics**' was originated from the necessity to manage, analyze, and understand the myriad amount of data using informatics tools. These data were deposited in public databases freely accessible via the World Wide Web. Before the end of HGP, the International Haplotype Mapping (HapMap) Project[3] – an effort to produce a genome-wide map of common human genetic variations with the aim to speed the search for genes that contribute to common diseases – was launched in November 2002. This project has successfully generated the data of over 3 million human single nucleotide polymorphisms (SNPs) from geographically diverse populations.[4,5]

The HGP has a great impact to the research and application in human molecular genetics, which finally leads to the origination of '**Genomics**' – a new discipline that studies functions and interactions of all the genes in the genome.[6] **Functional Genomics** is the division that involves the examination of global gene expression (transcriptome) and overall proteins (proteome) in the cells or their extracellular milieu. It is an extension to the understanding of genetic contributions to human health which gives rise to '**Genomic Medicine**'.[7,8] This new discipline not only provides an important insight into the biology of health and disease but also plays an increasingly important role in the development of new methods for prevention, diagnosis, monitoring, and treatment of diseases. It has started to fundamentally change the practice of medicine in the way that was not possible before and will revolutionize medicine in the 21st century.[6-9] The importance of the '**Genomic Revolution**' has been emphasized in two series of review articles recently published in The New England Journal of Medicine (November 2002 – September 2003) and the Mayo Clinic Proceeding (August 2002 – May 2004).

From Genetic to Genomic Medicine

The advances in molecular genetic techniques in the past few decades have assisted us to unravel more than one thousand monogenic (Mendelian) genetic disorders, which are caused by mutations of single genes. These diseases have a high-risk but segregate in rare families. Unlike monogenic disorders, common and complex genetic (previously classified as multifactorial) diseases result from susceptibility genes with only a minor individual effect on the disease *per se*. The diseases in this group are caused by interplay between multiple genes and environmental factors. As many of them run in families, they are thought to be inherited, but different from Mendelian disorders, since they do not show the definite inheritance patterns. The genetic variations contribute to susceptibility to these diseases causing increased individual's risk to diseases, but may not result in the diseases without environmental triggers. However, they are much more prevalent than monogenic diseases and are the focus of intense attention in current genetics and genomics research. The examples of diseases in this category include diabetes mellitus, hypertension, heart disease, cancer, autoimmunity, asthma, mental illness, neurodegenerative disorders, and many more.

Two main genetic approaches, linkage analysis and association study (Fig 1), have been complementarily used to detect the specific genetic regions or loci associated with the diseases, which can be used with candidate-gene and genome-wide studies. The known (parametric) or unknown (non-parametric) mode of inheritance may be applied in the linkage calculation. Linkage analysis is powerful for localization and identification of causative genes in monogenic disorders but it is less efficient for identification of susceptible genes in common and complex genetic diseases which occur

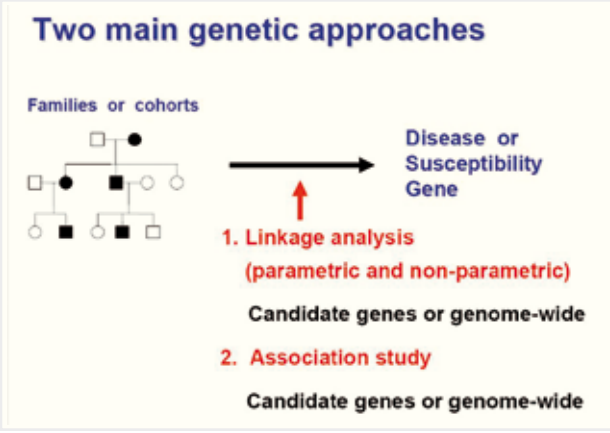


Fig 1. Two main genetic approaches, linkage analysis and association study, can be used for chromosomal localization and identification of disease or susceptibility gene.

from variations of several or many loci.

The availability of the human genome resources and the recent development of high-throughput genomic technologies (such as microarray) for simultaneous analyses of genomic variations, in combination with new analytical methods, have now made it possible to use a genome-wide association study (GWAS), which is the most powerful and efficient approach thus far, for identifying genetic variants associated with human common and complex genetic diseases (Fig 2).

GWAS became feasible because of the availability of large collections of cases and controls, in addition to the advancement in genetic technologies and statistical analysis methods. Recently, many common and complex genetic diseases and quantitative traits were successfully studied by GWAS and many more studies are in progress. At the initial stage of this technology, nearly 100 loci for nearly 40 common diseases and traits have been identified.[10] Publications on the use of GWAS for this group of diseases includes macular degeneration and exfoliative glaucoma, type 1 and type 2 diabetes, inflammatory bowel disease, prostate cancer, breast cancer, colorectal cancer, cardiovascular disease, neuropsychiatric conditions, autoimmune and infectious diseases, and others. These have provided new insights into disease etiologies and have suggested previously

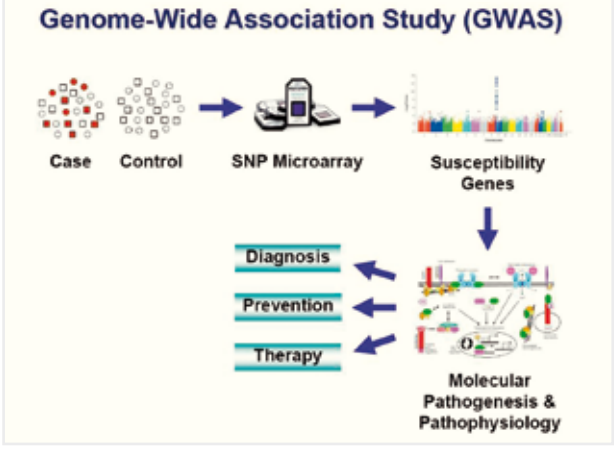


Fig 2. Genome-wide association study (GWAS) for identification of susceptibility genes in human common and complex genetic diseases.

unsuspected molecular pathophysiology pathways for common diseases useful for identifying new therapeutic targets and developing targeted interventions based on genetically defined risk.[10]

Genomic Revolution

Genomics makes its greatest contribution to medicine by revealing pathogenic and pathophysiologic mechanisms underlying the human common and complex diseases, which promisingly leads to the development of new approaches for prevention, diagnosis, and therapy.[7,8] The capability to rapidly analyze an individual's genomic sequence variation is useful for acquiring genetic information related to human health including susceptibility to diseases. Microarray-based technology (DNA chips) has currently been used for this rapid analysis. This information is important for determination of preventive measures for the disease that has genetic susceptibility, but has not yet occurred.

A better understanding of the multiple and interacting genetic components of disease pathogenesis and pathophysiology will make it possible to specifically design targeted therapies.[8,9] Moreover, it will be possible to customize drug and other treatments to accommodate both individual patient's inherited differences in the disease process and individual patient's genetic variations in their ability to metabolize drugs, which are the issues addressed by '**Pharmacogenomics**'. Genetic variations in the genes involved in drug metabolism, particularly the cytochrome P450 (CYP450) multigene family, encoding enzymes responsible for metabolizing most drugs used today, will affect their functions and patients' responses to the drug and the dose administered.[9] A rapid testing to determine individual patient's genotypes will guide treatment with the most effective drugs and reduce adverse reactions. This will lead to a paradigm shift from '**one-size-fits-all**' treatment to '**customized therapy**' and '**individualized medicine**'.

Genomic data and technologies will also accelerate the rate, reduce the cost, and increase the efficiency of new drug development. The targets of most drugs today are about 500 molecules.[9] The knowledge of genes involved in the disease process, pathophysiologic pathways, and response molecules will lead to the discovery of new drug targets. Ideally, the new drugs should aim at specific sites of cells and at a specific biochemical pathway or molecule implicated in the disease process and they should also cause fewer side effects than many current medicines.

Ethical and Societal Concerns

The promise of genomic revolution in medicine is unprecedented but this excitement is modest by public concerns regarding the potential misuse of genomic information and technologies. Several ethical, legal, and societal issues that must be addressed include the possibility of loss of personal confidentiality, social and employment discrimination, group stigmatization, and the more complicated issue of genomic determinism. From its first initiation, the HGP dedicated a proportion of about 5% of its funds toward identifying and addressing these issues arising from the availability of new information and capabilities.[9]

The incomplete understanding of the pathogenesis of common and complex genetic diseases leads to problems in the translation of genomic information into clinical

practice. The difficulties in identifying genetic susceptible loci and alleles of the diseases result in uncertainty in interpretation. Further research and technological development are still needed for many common and complex genetic diseases before the clinical applications will be possible. For the diseases that the clinical applications of genomic technologies are available, the provision of adequate counseling and support for individuals at risk is required for the presymptomatic screening.

To gain a full benefit and efficiently apply the genomic technologies, it is essential that the genomic knowledge and technological capabilities appropriate to each ethnic population and country or geographical area should be created and developed, because it has now been realized that different genomic variations causing the same diseases exist in each population. These appropriate genomic knowledge and technological capabilities should also be effectively transferred to the local health-care providers in each country by incorporating them into normal educational curriculums and training systems.

Future Trend

Routine generation of whole-genome sequences will greatly affect biomedical research and clinical care. The scientists who were involved in the HPG and who are studying genomics wish to have new technologies that can sequence the entire genome of any person for less than $1,000.[1] It has been predicted that within 5 years DNA sequencing technologies will be affordable enough that personal genomics will be integrated into routine clinical care.[11] On January 22, 2008, an international research consortium announced the '**1000 Genomes Project**', which is an effort to sequence the genomes of at least a thousand people from around the world to create the most detailed and medically useful picture of human genetic variation.[12,13] Personal genomes from two well-known scientists have recently been sequenced and reported.[14,15] When the technologies for whole-genome sequencing of any person become feasible, many benefits such as presymptomatic screening, genetic susceptibility and risk evaluation, disease prediction and prevention, and pharmacogenomic applications are anticipated. Other applications include ancestral tracing, personal identification and forensics, nutritional choice and advice, and reproductive assistance. The medical community may need to consider and provide guidelines for efficient routine use of personal genomic information, its effect to the health system, and ethical, legal, and social implications – in addition to those that have been addressed in the preceding projects. Two important questions concerning the genomic knowledge and technologies are: (*i*) how to efficiently and ethically use them, and (*ii*) how to make them economical and accessible, so they will be widely beneficial to most people.

ACKNOWLEDGMENTS

The author is a Thailand Research Fund (TRF) Senior Research Scholar (SRS). A part of the content in this article was presented at the ***TRF-SRS Academic Conference 2008 – 'Human Molecular Genetics Conference: Molecular Genetics of Complex and Common Genetic Diseases'***, September 29, 2008, Royal River Hotel, Bangkok, Thailand.

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