Future Medicine in the Post-Genome Age
—Targeting tailored medicine for hypertension—

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Abstract: The release of the draft sequence of the whole human genome in 2001 is still fresh in our minds. In the post-genome era, a key concept “tailored medicine for common diseases” is proposed with a view to future medicine. The term “tailored medicine” means personal and optimized medical service for each individual, with low risks and high quality. Single nucleotide polymorphisms (SNPs), personal nucleotide alterations in the human genome, provide important information to clarify the pathogenesis of common diseases and advance the development of tailored medicine. We have examined various interactions between SNPs and hypertension or hypertensive complications to demonstrate genetic predisposition to salt sensitive hypertension in Japanese people. Furthermore, several preliminary results suggest that the effect of environmental factors was significantly different according to genotypes of SNPs. Achieving the stage of tailored medicine, physicians may in the future refer to the SNPs data of the patient as an aid to daily medical care.

Key words: Genetics; Polymorphism; Human genome; Renin-angiotensin system; Salt sensitivity

Introduction

The draft sequence of the entire human genome released in the two leading science journals, Nature and Science, in February 2001 is still fresh in our minds. Genome is a general term denoting a basic set of DNA strands containing genes composed, by nature, of the four bases: guanine, adenine, thymine and cytosine. As is widely known, an entire human genome comprises approximately three billion base pairs, which, as elucidated by Drs. Watson and Crick, form the characteristic double-stranded helical structure. It was generally believed that approximately one hundred thousand genes are arranged on a human genome, but once the base
sequence was actually determined, it turned out that the number is limited to about thirty thousand genes. The published completion of a draft sequence has nevertheless revealed an arrangement of only a little more than 90% of constituent bases, whilst research on the roles of genes and their bearing upon disorders and disease states has just begun to take shape.

It is said that the oncoming era will be an age of analyses of the transcriptome, a general term for transcription products, or of the proteome, a general term for translation products. However, accurate understanding of the significance of the genome per se should be given priority when it comes to carrying out these approaches. We would also like to stress that the term “post-genome age” does not connote that genome analysis is completed; it only connotes that the human genome has been elucidated sufficiently enough to allow entry into a whole new paradigm of medicine.

Tailored Medicine

The term “tailored medicine” has been proposed as a keyword for the post-genome era. Tailor-made medical care means instituting the medical care that is best suited to the constitution of any given individual patient and is generally thought to represent medical care of the twenty-first century as distinct from the current form which is uniform for all patients.

Regarding hypertension, by way of an example, tremendous efforts have been devoted to the control of this disorder because of a high incidence of strokes, especially cerebral hemorrhage, in this country. These efforts led to success in achieving a substantial reduction in the incidence of cerebral hemorrhage through lifestyle correction and the development of various antihypertensive drugs. With the arrival of the super-aging society, however, the decline in incidence has already reached its ceiling and mortality from cardiovascular disorders has reportedly taken an upward turn. In the quest for a powerful solution for reducing deaths from cardiovascular disorders, current research is being directed toward the elucidation of the pathogenesis of hypertension by gene analysis, the use of tailor-made medical care utilizing this information, development of new drugs based on genomic information, and exploration of the applicability of gene therapy.

Gene Analysis and Genetic Diagnosis

The form of hypertension that causes most cardiovascular diseases is essential hypertension, hence of unknown etiology. Three strategic techniques are currently used in analyzing the genes responsible for essential hypertension, i.e., the linkage analysis, which analyzes familial aggregation of the disease using a pedigree; the sibling pair analysis, which analyzes identity by descent using affected or discordant sib-pairs; and the case-control study, which compares the genetic backgrounds of hypertensive subjects with those of normotensive subjects (Fig. 1). Linkage analysis using pedigrees is markedly useful in the study of rare monogenic hypertension such as Liddle’s Syndrome and glucocorticoid-remediable aldosteronism, and has succeeded in identifying the gene mutations that cause disorders such as epithelial amiloride-sensitive sodium channel gene.1)

A clear causal relationship exists between a gene and the development of a monogenic disorder inasmuch as hypertension definitely develops in the presence of a gene mutation. Gene analysis may thus be said to constitute genetic diagnosis in monogenic disorders. In the case of essential hypertension, which is a disorder of multifactorial causation, on the other hand, there is no clear causal relationship between an altered base sequence of the gene and hypertension. In hypertension, gene analysis merely demonstrates that the presence of a certain type of gene indicates a higher probability for developing the disorder. This type of gene, which bears an increased relative risk, is called a disease-susceptible gene, and the
are again in the limelight. We focused our attention on nucleotide polymorphism of the renin-angiotensin system using this approach. Our study has revealed that TT type gene polymorphism involving amino acid substitution of threonine for methionine, called M235T polymorphism at exon 2 of the gene coding angiotensinogen, has bearing on the family history of hypertension and on the non-dipper type hypertension characterized by a minor nocturnal decrease in blood pressure.2) With regard to the renin-angiotensin system, a thrifty gene hypothesis has been proposed. This hypothesis supposes that the renin-angiotensin system was originally essential for retention of sodium and water within the bodies of human ancestral species evolved from lower aquatic life,3) and goes on to suggest that the advent of our satiated consumer age may have led to the increases in hypertensives and patients with cardiovascular complications. In support of the hypothesis, one may note that the TT type accounts for 100% of chimpanzees, for 90% of an African hominid thought to be a close ancestor of human beings, and for more inter-individual differences in base sequence observed in the genome are referred to as genetic polymorphism. The ABO blood types are a good example of nucleotide polymorphism. Although peptic ulcer is more common among persons of blood type O, not all individuals with blood type O are predisposed to peptic ulceration; likewise, it should be understood that the results of analyses of genetic polymorphisms indicate a risk for hypertension but do not necessarily diagnose hypertension.

**Gene Analysis of Hypertension and Gene-Environment Interactions**

Large-scale genome screenings using sib-pair analyses have been conducted in Europe and the United States. In essential hypertension, any relevant single gene polymorphism appears to exercise a comparatively minor influence. However, it has been proven that it is difficult to isolate susceptible genes for hypertension even if thousands of sib-pairs are collected. Case-control studies comparing a hypertensive subject group with a normotensive subject group are again in the limelight. We focused our attention on nucleotide polymorphism of the renin-angiotensin system using this approach. Our study has revealed that TT type gene polymorphism involving amino acid substitution of threonine for methionine, called M235T polymorphism at exon 2 of the gene coding angiotensinogen, has bearing on the family history of hypertension and on the non-dipper type hypertension characterized by a minor nocturnal decrease in blood pressure.2) With regard to the renin-angiotensin system, a thrifty gene hypothesis has been proposed. This hypothesis supposes that the renin-angiotensin system was originally essential for retention of sodium and water within the bodies of human ancestral species evolved from lower aquatic life,3) and goes on to suggest that the advent of our satiated consumer age may have led to the increases in hypertensives and patients with cardiovascular complications. In support of the hypothesis, one may note that the TT type accounts for 100% of chimpanzees, for 90% of an African hominid thought to be a close ancestor of human beings, and for more
than 70% of Japanese. This may explain why salt-sensitive hypertensives are more common among Asian and Negroid people. In fact, a large prospective epidemiological survey on Caucasians with normal high blood pressure revealed that \( TT \) type subjects on an ordinary diet had a higher probability of developing hypertension whereas \( TT \) type subjects who actively followed a low sodium diet program had increased blood pressure less frequently than subjects with \( MT \) or \( MM \) genotype.\(^4\) It would thus be advisable, using the application of the angiotensinogen gene \( M235T \) polymorphism to tailored medicine, for \( TT \) type subjects to be positively guided toward low-sodium intake while an earlier institution of antihypertensive drug therapy should be considered for subjects with \( MT \) or \( MM \) genotype.

The relationship between angiotensinogen gene polymorphism and salt sensitivity is a good example indicating the importance of gene-environment interactions. As for the interrelation of salt sensitivity and genes, it has recently been revealed that genetic polymorphisms of \( \alpha \)-adducin, aldosterone synthase, \( G \) protein \( \beta_3 \) subunit, etc. are also related to salt sensitivity.\(^5\) Interestingly, all allele frequencies of salt sensitive genes are higher in the Japanese population than in Caucasians, suggesting that the Japanese may be a hypertensive race with an intrinsically high sensitivity to salt (Fig. 2).\(^6,7\) A strict low sodium diet would be the first step to tailor-made medicine for Japanese people.

Furthermore, based on the results of genetic polymorphisms of endothelin 1 and \( \beta_2 \) adrenoceptors, it has also been revealed that blood pressure elevation associated with obesity varies with genotype.\(^8\) It thus follows that obese individuals liable to high blood pressure may have to be positively guided to weight reduction. Other findings from gene analyses include the fact that angiotensin-converting enzyme gene polymorphism constitutes a potential hypertensive risk for males alone\(^9\) and that some young females with angiotensin II type 2 receptor gene polymorphism are genetically invulnerable to hypertension. From these findings, it should be understood that essential hypertension is characteristically an intricate disease state etiologically composed of environmental and genetic factors and that correctly ascertaining the particular environment within which a given genomic information is meaningful will lead to tailored medicine.

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Fig. 2 Allele frequency of genes related to salt sensitivity

---Japanese vs. Caucasians---

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Pharmacogenetics

Pharmacogenetic approaches are another way of utilizing gene polymorphism. It has become increasingly clear that the effects and incidence of adverse reactions to drugs vary widely with genetic polymorphisms ranging from enzymes directly involved in drug metabolism in individuals to the above-mentioned renin-angiotensin system. The utilization of this information is expected to be most powerful in the selection of effective antihypertensive drugs as well as in warding off serious adverse reactions. We have demonstrated that the efficacy of angiotensin-converting enzyme inhibitors administered for prevention of post-PTCA coronary artery restenosis varies with the genotype of insertion/deletion (I/D) polymorphism of the angiotensin-converting enzyme (ACE) gene (Fig. 3). Gene therapy that corresponds to the polymorphism in the promoter region may prove effective where gene polymorphism is involved in transcriptional control. Gene therapy for arteriosclerosis obliterans, a complication of hypertension or diabetes, has been initiated at our department, and we also intend to make use of genetic data in gene therapy for ischemia in the heart or brain.

Millennium Project

In gene analysis, the collection of accurate clinical information and of adequate specimens constitutes a key factor in the clarification of the relationship between a subject’s clinical information and gene polymorphism. For hypertension for which genetic relative risk is low, cases and controls that represent both ends of a general population, e.g., severe hypertensives and apparent normotensives, are required to enhance statistical power. Ideally, a group of subjects that form a population should be gathered within the same geographical region.

To pursue this type of large-scale case control study and genoepidemiologic research, a national cooperative study system, which has been designated as a millennium project, has been organized and preparations for the elucidation of genes sensitive to hypertension and other lifestyle-related disorders are underway. More than a hundred thousand single nucleotide polymorphisms (SNPs) have already been identified out of the entire human genome, and genomic screening utilizing these SNPs are about to start. Several dozen hypertension-sensitive genes are expected to be verified by the year 2005. Therefore, tailored medicine based on the information on gene polymorphisms sited above may perhaps be in practical use at clinics by the year 2010.

Ethical Problems and Perspectives

Ethical issues are an important factor in the process of conducting these gene analyses and cannot be avoided. The triministerial joint ethical guidelines for human genome analysis were issued in March 2001, under which the preparation of a research protocol and obtaining informed consent are mandatory. The confidentiality of personal information must be maintained, and further, providing an accurate explanation to study subjects, attaining their understanding of inheritance, genes and gene polymorphism, giving a full explanation and obtaining their consent regarding retention of specimens and handling of analytical results are all compulsory.
Another task lies in the technological innovation for determining a vast number of genetic polymorphisms. While conventional techniques involved comparatively large quantities of specimens and manipulations, for example, enzymatic processing and electrophoresis, less costly procedures for genotype identification such as the TaqMan PCR method and the Invader technique requiring minute quantities of specimens are under development. Once information on the minimum number of polymorphisms needed to analyze Japanese subjects is gained, together with the development of bioinformatic, the development of DNA chips that enable an instantaneous analysis of information on several hundred thousand gene polymorphisms will no longer be a dream. Moreover, once such an era is inaugurated, individuals may carry their personal gene polymorphism information with them like credit cards, to which the attending physician may refer to provide daily living guidance and individualized drug selection.

Objectifying tailored medicine not only effectuates optimal medical care but is also expected to lead to the prevention of malpractice and reduced medical expenses. Practically no one had predicted such widespread use of cell phones and video games throughout the country before the present-day developments in information technology were realized.

In the most desirable medical care of the post-genome age, gene analysis and gene therapy will not sound peculiar to patients or to general practitioners and will probably be handled matter-of-factly.

REFERENCES