Pharmacogenomics in Asia

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It is well known that genetic polymorphisms, such as SNPs, vary between races so that not only Western populations' pharmacogenetic/pharmacogenomic data but also data from Asians are viewed as vital to drug development and clinical practice. For this report, the current state of pharmacogenetic/pharmacogenomic-related activities in five Asian countries (China, Japan, the Republic of Korea, Singapore, and Taiwan) were researched and analyzed. The results show that there are multiple efforts underway in all of these countries, including the examination of guidelines, the implementation of projects to establish foundations for pharmacogenetics/pharmacogenomics, and several clinical trials, that have hardly been recognized up to now.

Introduction

It is well known that there are ethnic differences among genetic polymorphisms, such as SNPs. For example, of the 452 SNPs identified in cytochrome P450 (CYP) by the Pharma SNP Consortium, 244 could be considered unique to the Japanese [1]. Therefore, not only pharmacogenetic/pharmacogenomic (PGt/PGx) data from Western populations (Caucasian) but also from Asian populations should be viewed as vital to drug development and the clinical practice of medicine in the genomic era. For this report, the current situation of drug development incorporating PGt/PGx and programs aimed at establishing an infrastructure for PGT/PGx research in Asia will be discussed. The information presented was collected while interacting with experts in PGt/PGx from China, the Republic of Korea, Singapore, and Taiwan, as well as from published material [2].

Guidelines on pharmacogenetics/ pharmacogenomics

The US Food & Drug Administration (FDA) published the 'Draft Guidance for Industry on Pharmacogenomic Data Submissions' on November 3, 2003, to encourage the use of PGt/PGx in drug development [101]. Most pharmaceutical companies see this as a positive step.

In Japan

A draft proposal entitled 'Submitting clinical trials information in which pharmacogenomic approaches were used to the regulatory agency for making a guidance document for pharmacogenomic approaches on pharmaceutical developments' has also been issued by the Japanese Ministry of Health, Labor and Welfare (MHLW) on June 8, 2004 [102,103].

There have been two notifications related to PGt/PGx that have been issued by the MHLW. There are the 'Clinical Pharmacokinetic Studies of Pharmaceuticals' notification, which was released on June 1, 2001, and the 'Methods of Drug Interaction Studies', issued on June 4, 2001. Both notifications refer to genetic polymorphisms.

In Taiwan

The 'Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data' (2000) and relevant notifications were issued by the Department of Health (DoH) of Taiwan, which are related to PGt/PGx and are expected to encourage pharmaceutical companies to involve Asia in multinational clinical trials that incorporate genetic polymorphism analysis.

Although no specific guidelines or notifications referring specifically to PGt/PGx have been released in Asia to date, most institutions have begun the consideration of developing guidelines.

Guidelines on bioethics

When the General Conference of the United Nations Educational, Scientific and Cultural Organization (UNESCO) adopted the 'International Declaration on Human Genetic Data' in 2003, awareness surrounding bioethics issues seemed to be changing in most parts of the world in response to the rapid advances in human genome research [104]. The importance of bioethics is widely recognized in Asia, although social values and traditions are different between Asian and Western countries.

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future medicine

In China

At present, no bioethics-related law has been enacted; however, it has been reported that they will follow treaties made by the United Nations and UNESCO, in principle.

In Japan

There is one law and four ethical guidelines that are significant to the promotion of PGt/PGx: the 'Personal Information Protection Law' (May 23, 2003); the 'Fundamental Principles of Research on the Human Genome' (June 14, 2000); the 'Ethics Guidelines for Human Genome/Gene Analysis Research' (March 29, 2001); the 'Ethical Guidelines for Performing Human Genetic Testing, Contracted to the Japan Registered Clinical Laboratories Association' (April 10, 2001); and the 'Guidelines for Genetic Testing', issued by the Japan Society of Human Genetics, Council Committee of Ethics (August, 2003) [105,106]. Among the above guidelines, the 'Ethics Guidelines for Human Genome/Gene Analysis Research' has proven to be the most important. This guideline, which regulates human genome/gene analysis, requires compliance by researchers working in these fields. The key feature is the emphasis of transparency in order to promote scientific research. Needless to say, stressing ethics, such as informed consent, confidentiality and having a ethics committee, is essential. Clinical studies and postmarketing surveillance are regulated by the Pharmaceutical Affairs Law and are, as such, excluded from the guideline. This guideline is now under review, while the Personal Information Protection Law shall take effect as of April 1, 2005.

In the Republic of Korea

A 'Bioethics and Biosafety Law' was passed by the National Assembly in December 2003 after debates that lasted for more than 4 years. The law will become effective in January 2005, and a National Bioethics and Biosafety Review Committee will be established under direct control of the President. Furthermore, the 'Research Guideline for Functional Analysis of the Human Genome', which was published in June, 2002, contains autonomy, or the right to self-determination by the potential subjects, and the protection of the individual's genetic privacy, in addition to outlining the responsibilities of the Institutional Review Board.

In Singapore

There is the 'Ethical Guidelines for Gene Technology' for genetic testing guidance in clinical practice, which was issued by the National Medical Ethics Committee in February, 2001 [107].

In Taiwan

There are some general bioethics guidelines, such as the 'Guideline on the Collection and Use of Human Samples for Research Purposes'. However, there are no nationwide guidelines on bioethics concerning human genome/gene research or genetic testing at present. Therefore, comprehensive research guidelines for ethical issues related to human genome studies, including PGt/PGx, are currently under discussion at the DoH.

Promotional activities for pharmacogenetics/pharmacogenomics

Various activities, such as funding, examination of effective use, information provision and enlightenment, are performed country-by-country at the governmental and private-sector levels in order to promote PGt/PGx. These are described in further detail below.

In China

The Ministry of Health is funding disease genomics and Chinese PGx research work. In addition, the Chinese Pharmacology Society's Committee on Clinical Pharmacology is to consider the measures to be taken to make use of PGt/PGx [108].

The Chinese Human Genome Center is holding an international study meeting to promote PGt/PGx in conjunction with the Environmental and Occupational Health Sciences Institute (a joint institute of the Robert Wood Johnson Medical School and Rutgers University in the USA) [109,110].

Lastly, a Forum of Chinese Pharmacogenomics was held by the National Natural Science Foundation of China and the Bureau of Science and Technology to discuss the application of PGt/PGx to clinical practice.

In Japan

Three organisations have been active in promoting PGt/PGx: the MHLW, the Japan Health Sciences Foundation, and the Japan Pharmaceutical Manufacturers Association. The MHLW has held an internal study meeting with attendants from both the MHLW and the Pharmaceuticals and Medical Devices Agency to consider the measures that should be taken to make use of PGt/PGx. Working groups from the Japan Health Sciences Foundation has conducted

investigations on genomics, issued several reports, and organized a symposium to promote PGt/PGx, which was held in Tokyo in April, 2003 [111]. The Japan Pharmaceutical Manufacturers Association (JPMA) held a symposium to promote PGt/PGx properly on June, 2004, in Kyoto [112]. They are also drafting an independent guidance on clinical trials that incorporate PGt/PGx.

In the Republic of Korea

Several agencies and companies are involved in promoting PGt/PGx research in the Republic of Korea. The Ministry of Health and Welfare is funding the Korean Pharmacogenomics Research Network (KPRN), the disease genomics, pathogenic microbe genomics and proteomic research center [113]. The Korean Food & Drug Administration (KFDA) is preparing guidelines for the application of PGt/PGx for drug regulation [114], and the Ministry of Science and Technology is funding the National Research Laboratory for Pharmacogenomics and is further planning on funding research in toxicogenomics in nonclinical fields [115]. In addition, the Pharmacogenomics Research Study Group is arranging regular research seminars and symposia, and several international symposia have been held in the country, including:

- Yonsei Biomedical Symposium, Seoul (February, 2003)
- Pharmacogenomics: Impact on Clinical Trial, Seoul (October, 2003)
- Pharmacogenomics: A Step Toward Personalized Pharmacotherapy, Busan (February, 2004)

In Taiwan

The Center for Drug Evaluation is holding internal taskforce meetings to look into current PGt/PGx-related research projects and clinical trials, as well as evaluating methods to promote cooperation between the DoH, the Ethics, Legal and Social Implications (ELSI) Program, and the Center for Drug Evaluation in order to enact PGt/PGx-related regulations and laws [116].

Several symposia and workshops have also been hosted in Taiwan, including:

- Taipei Science and Technology Law Forum – Legal Reform in Response to the Bio-Tech Revolution in the 21st Century (August, 2002)
- Clinical Research Seminar Series – Pharmacogenomics and Population Pharmacokinetics by the Foundation of Medical Professionals Alliance in Taiwan (FMPAT), Taipei (December, 2002)
- Workshop on Biomedicine Research and Bioinformatics by GigiGenomics Co., Taipei (March, 2004)

Projects to establish a foundation for pharmacogenetics/pharmacogenomics

The research shows that many projects to establish a foundation for PGt/PGx are underway in Asia; many of which have hardly been recognized up to now.

In China

The Research Center for Medication in Minorities began in 1993 to apply PGt/PGx to clinical practice with an eye on ethnic differences for drug metabolism and the response in Chinese minorities. Many more projects, such as the Chinese Pharmacogenomics Research Project, the Project on the Relationship between Genomics and Severe Diseases, the Pharmacogenomics and Modernization of Chinese Herbs, and the Individualization of Drug Therapy for Patients with Hypertension, have taken place in China since 2001.

In Japan

Researchers in Japan have contributed to and are working on the International HapMap Project, the Project on Realization of a Medical Care System in Accordance with Genetic Information and the Pharma SNP Consortium [117]. Groups in China and Taiwan are also working on the International HapMap Project.

In the Republic of Korea

The KPRN and the National Research Laboratory for Pharmacogenomics were initiated in 2003 to apply PGt/PGx to clinical practice.

In Singapore

As Singapore is a pluralistic society, much PGt/PGx research focuses on the ethnic differences among Chinese, Caucasians, Indians, and Malays. Some research projects have been carried out at the National University Hospital and the National University of Singapore. The National University Hospital Pharmacogenetics Research Projects, the national DNA bank and the Singapore Tissue Network were also set up in 2002.

In Taiwan

The National Science Council and the DoH began the National Research Program for Genomic Medicine in 2002, and the PGt/PGx is set to be one of the major focuses in this program in the next 5 years, beginning in 2004. The Super

Highlights

- There are no specific guidelines or notifications on PGt/PGx in Asia to date; however, most countries have begun serious consideration of developing guidelines.
- The importance of bioethics is widely recognized in Asia and various types of ethical guidelines have been issued in each country.
- The 'Bioethics and Biosafety Law' was passed by the National Assembly in the Republic of Korea in December 2003 and will be effective in January 2005.
- Every country is educating people via various symposia and workshops.
- There are many projects working toward establishing a foundation for PGt/PGx in Asia.
- DNA banks have been established in most countries.
- Many clinical trials have already been conducted in every country.
- There are already some examples of practical use of PGt/PGx.

Control Genomic Database was also founded in 2002 to create a control pool that enables the comparison and contrasting of various local diseases, and more than 3000 blood samples have been collected, to date. In addition, the Pharmacogenomics Program at the Institute of Biomedical Sciences, Academia Sinica, and the Hepatitis B and C Pharmacogenomic Project are ongoing.

Recent developments in the pharmaceutical industry

In Japan

According to the results of a questionnaire survey given by the JPMA on experiences in clinical trials involving PGt/PGx, over 50 clinical trials have been performed by companies belonging to this organization. Although the majority of them concern metabolic enzymes, some concern drug reactions. At present, there are three examples of the use of PGx information on labels for prescribing information in Japan. They are trastuzumab, rituximab, and imatinib mesylate. Diagnostic kits are also under development.

In the Republic of Korea

Several bioventures are applying genotyping to clinical practice and multinational pharmaceutical companies are sponsoring several clinical trials, searching for any relationship between drug efficacy or adverse effects and specific genotypes.

In Singapore

A total of 20 clinical trials incorporating PGt/PGx, 10 of which are Phase I trials, 4 are Phase II trials and 6 are Phase III trials, were iniated by both industry (16) and hospitals or research institutes (4) from 2003 through to the first quarter of 2004, which account for approximately 15% of all trials.

In Taiwan

A number of multinational Phase III and post-marketing clinical trials, including blood sample collection for PGx analysis and the evaluation of pharmacokinetic-related genetic polymorphisms, have been started. A proprietary DNA-based diagnostic technology has already been developed using PGx approaches to determine which patients and carriers are susceptible to the conventional therapy and combinational therapies involving interferon drugs for the treatment of hepatitis C.

Expert opinion

Which polymorphism people are interested in and from what studies advances have been made might depend on the frequencies of the polymorphism, the number of patients in the area, and the diseases each country is interested in. For example, the frequency of poor metabolizers of CYP2C19 in the Japanese population has been reported to lie in the range of 18–23%, while only 2.5–6% of Caucasians are poor metabolizers. In addition, the high incidence of stomach cancer in Japan presents a larger health-care problem. Therefore, many reports exist on CYP2C19 for *Helicobacter pylori* eradication therapy in Japan. Although the polymorphisms that each researcher or country is interested in might be different, international cooperation is necessary to promote PGt/PGx globally.

Outlook

Regulatory agencies are getting ready to prepare PGx guidance documents in the USA, Europe, and Japan. It is necessary to respond to them in Asia so that people in every country can enjoy the benefit of medicine based on PGt/PGx. This paper shows that the pool of basic data and the building of the necessary infrastructure is beginning to be realized in PGx-based medicine in Asia. It is expected that all of the countries will make collaborative efforts toward global harmonization with each other.

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