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EELS (Ethical, Economic, Legal & Social) ARTICLE

Pharmacogenomics in Japan

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It is clear that in order for scientific advancement to become a reality, the exchange of views and information among people with different backgrounds is necessary. Thus, international cooperation is important for the global promotion of pharmacogenetics and pharmacogenomics. Unfortunately, information from Asia still seems to be insufficient, even in the globalized world of science and medicine. For this reason, we would like to provide an overview of pharmacogenomics in Japan.

INFRASTRUCTURE FOR PHARMACOGENOMICS LED BY THE GOVERNMENT

The Japanese government started the Millennium Project in April 2001 to focus on technological innovation concerning three subjects: computerization, an aging-society, and environmental issues. These points are expected to become more important and urgent to the Japanese economy as time progresses, hence any positive developments resulting from the project could brighten the outlook for the future. Research and analysis on the human genome was conducted as one of the projects. Data on 195 059 SNPs have been obtained, and to date, 84 557 of them have been analyzed for their allele frequency using samples from a general population of 752 Japanese. This includes around 6000 coding SNPs (cSNPs) for about 180 pharmacokinetic-related enzymes.[1] These data are expected to have a positive effect on pharmacogenomic research and clinical studies in the future.

In October 2002, the International Hap Map Project was started for haplotype mapping. Participating countries include the USA, UK, Japan, Canada, and China. A total of 200–400 blood samples from Mongolian, Caucasian, and Negro donors are to be collected for haplotype mapping over the next 3 years. Japan will bear one-quarter of the responsibility for analysis. The data will be published in 2004, and their clinical application to pharmacogenomics is expected.

The Personalized Medicine Project (Biobank Japan Project), aimed at optimizing drug therapy based on elucidating a patient's genetic constitution, was launched in June 2003. Participants in this project consist of eight medical institutes, 37 hospitals, two research institutes, and the new Biobank Japan. A total budget of 20 billion yen will be invested in this project by the government over a 5-year period, starting in 2003. The first order of business for the project will be to elucidate SNPs tied to drug efficacy as well as those related to the onset of adverse reactions and diseases. Over 40 such diseases will be studied, including cancer and diabetes. The research will be conducted using DNA and serum obtained from approximately 300 000 patients who have given their prior, informed consent for the project.

In order to promote sample collection, the placement of trained medical coordinators in the 37 hospitals involved is now under consideration. Security measures for the computer systems used are also being considered. These measures include fingerprint authorization as well as a system by which a computer will destroy itself if someone makes repeated, unsuccessful attempts to access restricted areas of the databases of the participating institutes.

Some experts say that the Personalized Medicine Project should be initiated only after nationwide discussion. At the same time, high expectations prevail because of the success of the Millennium Project. The promise held by the innovative analysis techniques and the ethical approach also have people excited about the project. However, concerns have been expressed over the paternalistic attitude many Japanese physicians still harbor. Some believe that because of this attitude, informed consent will not become a popular and widespread practice. In the wake of the various projects relating to the human genome and genes form the entire Japanese population, though, the health care environment in Japan is expected to eventually reform.

BIOETHICS

The Personal Information Protection Law was legislated in May 2003. It has been suggested that this law does not apply to fields of scientific research or matters concerning public health and hygiene. However, many feel that it is in these areas where the law is most necessary. At the express request of the Japan Medical Association (JMA), the Upper House Special Committee on Personal Information Protection stated in a subsidiary resolution that immediate consideration would be given to a separate law for fields such as health care. This consideration includes research, development, and application in fields where public cooperation is vital for the establishment of advanced technologies (such as gene therapy) and where a high level of protection

for personal information is sought by the public.

There are several ethical guidelines significant to the promotion of pharmacogenomics in Japan, including the following:

- Fundamental Principles of Research on The Human Genome (June/2000)
- Ethics Guidelines for Human Genome/gene Analysis Research (April/2001)
- Guidelines for Genetic Testing, by The Japan Society of Human Genetics, Council Committee of Ethics (August/2003)
- Ethical Guidelines for Performing Human Genetic Testing Contracted to the Japan Registered Clinical Laboratories Association (April/2001)

The second guideline is the most important among those listed, requiring compliance by all researchers in these fields. The basic policies are as follows: (1) respect for human dignity, (2) adequate prior explanation and consent by one's own free will (informed consent), (3) complete protection of personal information, (4) research conducted shall be useful to society and shall contribute to human intellectual advancement, health, and welfare, (5) priority shall be placed on the protection of individual human rights rather than social/scientific benefits, (6) assurance of study adequacy by preparation of and compliance with study protocols based on the guideline after their review and approval by an independent ethical review board, and (7) assurance of study legitimacy by third-party monitoring of study performance at each site and by publishing study results. In total, 153 research organizations, including universities, national and public institutions, hospitals, and businesses, have been registered as of October 2003. The terms 'human genome/gene analysis,' as used in the guideline, include analysis of germline mutation or polymorphism, but not that of somatic mutation, which includes cancer, gene expression analysis, or proteomics. Clinical studies and postmarketing surveillance are regulated by the Pharmaceutical Affairs Law and are thus excluded from the guideline.

PHARMACEUTICAL LAWS AND REGULATIONS

There are two notifications related to pharmacogenomics issued by the Ministry of Health, Labour, and Welfare. One is 'Clinical Pharmacokinetic Studies of Pharmaceuticals (June 1, 2001)' and the other is 'Methods of Drug Interaction Studies (June 4, 2001).' Both of them are concerned with genetic polymorphisms. The necessity for the accumulation of know-how on pharmacogenomic methods and the creation of an organization for this purpose is also described.

ESTABLISHMENT OF PHARMACOGENOMICS PLATFORMS BY INDUSTRY

Over the past few years, working groups of the Japan Health Sciences Foundation (JHSF) have conducted investigations on genomics and issued several reports. The JHSF then played the role of 'compass,' providing direction for the development of pharmacogenomics in Japan. A conference entitled 'Symposium on Genomic-based Medicine 2003' was held by the JHSF in April 2003.

In September 2000, 43 member companies of the Japan Pharmaceutical Manufacturers Association established the Pharma SNP Consortium to conduct pharmacokinetic research on Japanese gene polymorphism. Blood samples donated by 752 Japanese volunteers were used in a frequency analysis of 4272 SNPs from 202 genes associated with pharmacokinetics, including cytochrome *P*450 (CYP), transporter, and esterase. Function analysis of the gene products of some CYPs and transporters, along with their variants, were also conducted.[2] Some of these findings have already been published, and others will be published shortly. Cell lines were also established from the samples and deposited in the Health Science Research Resources Bank.

PHARMACOGENOMICS IN DRUG DEVELOPMENT

The report, 'Clinical Application of Pharmacogenomics,' published by the JHSF in April 2003, describes the current situation and issues concerning pharmacogenomics in Japan. It also lists the results of a questionnaire survey on clinical development using pharmacogenomics that was conducted in Japanese companies.[3] The questionnaire was mailed to its 91 associate members, and the 44 that were returned were used for analysis.

The present status of clinical development using pharmacogenomics in Japan is as follows: 16 companies are investigating or are scheduled to investigate the effect of genetic polymorphism clinically; four clinical studies on pharmacokinetics are underway, and six studies are planned for the next couple of years. Three clinical studies are underway on pharmacodynamics, and seven studies are planned. Five companies plan prospective studies for their marketed products. The reason why most other members are not planning such studies is that they have no appropriate candidates as yet. Seven companies have already established an organizing system for managing personal information, 15 have started considering such a system, and three were considering entrusting this to an outside company. Among the questionnaire items, questions concerning the current issues surrounding genotyping resulted in the following replies (from more than 50% of companies): 'to get an understanding of genotyping' and 'document preparation related to the informed consent,' these replies were followed by 'relationship with ethics guidelines,' 'acquisition of an agreement for the necessity of conducting genotyping in the company,' and 'acceptance of genotyping by Institutional Review Boards.' Many companies proposed education and the establishment of guidelines as measures to address such issues. Others suggested that the government should positively promote participation. What must be stressed is that the appropriate people should make an effort to protect genetic information and human rights suffi-

ciently, make the information public, and thereby obtain public acceptance. Others looked forward to sharing an understanding and cooperation in order to apply the data to pharmacogenomics. As it is unclear to what extent the medical environment and infrastructure are prepared for pharmacogenomics, there is a fear of uncertainty about the extent to which information or established diagnoses can be applied clinically. Thus, the government is required to prepare the infrastructure, while pharmaceutical companies positively promote clinical studies incorporating pharmacogenomics, since it is their mission to supply better drugs by making use of the latest scientific advances.

EXAMPLES OF PHARMACOGENOMICS

Immuohistochemistry and fluorescent *in situ* hybridization tests, used to select patients to whom trastuzumab should be administered, are covered by health insurance and have already been used in clinical practice.

Troglitazone, a drug for the treatment of type II diabetes, was forced to be withdrawn from the market in March 2000 due to liver toxicity. A total of 68 SNPs in 51 candidate genes from the blood samples of 110 patients were analyzed. The results indicated that SNPs in the metabolic enzymes, GSTT1 and GSTM1, might play a role in the development of this liver toxicity.[4]

A method for predicting the therapeutic effects of imatinib mesilate by gene expression in each subject has been developed.

Clinical trials to investigate the therapeutic effects of gefitinib based on changes in gene expression have been performed since 2001 and projects to identify SNPs related to acute lung injury have just started.

Projects to identify SNPs related to the effectiveness and adverse reactions of pioglitazone, an insulin-sensitizing agent, have begun. Any discovery should pave the way to tailor-made medicines as well as new drug development.

Omeprazole and lansoprazole, proton pump inhibitors, are metabolized mainly by CYP3A4 and CYP2C19. Genetic polymorphisms in CYP2C19 affect these pharmacokinetic profiles. The frequency of CYP2C19 as a poor metabolizer (PM) has been reported to range from 18 to 23% in Japan. PM or an extensive metabolizer (EM) in patients is determined on an individual basis, and their relationship with the efficacy and safety of the long-term administration of these products should be investigated via postmarketing surveillance.

Genetic polymorphisms in MxA and MBL affect responses to interferon in patients with hepatitis C. Development of a genetic test for them on the DNA chip is ongoing.

Genetic polymorphisms in the promoter region of UGT1A1 affect the severe toxicity of irinotecan. Development of a genetic test for them is ongoing.

The pharmacogenomic approach to drug research and development by Japanese companies is lagging compared to that of European and American companies, although it seems some clinical trials are being performed based on SNP data obtained in Japan. We strongly hope that the private sector in Japan will face the challenges of using pharmacogenomics in drug development. The understanding and support of clinical investigations is just getting underway. The institution of translational research centers may be necessary, and the importance of public acceptance cannot be underestimated. Research through reasonable and flexible use of the guidelines for genome research can be accomplished without compromising ethics. The incorporation and resolution of all these issues will allow us to make breakthrough advancements for a brighter, healthier future, both for Japan and worldwide.

DUALITY OF INTEREST

None declared.

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