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Policy and Attitudes towards Collection of Personal DNA in genetic databases in Japan

Abstract

This paper presents the results of a public opinion research conducted in Japan on the willingness of persons to contribute their DNA to a genetic database, and the reasons behind their choices. The results are discussed in light of the Act Concerning Protection of Personal Information issued in 2003, and with reference to genetic database projects that have been conducted in Japan. There appears to be increasing concerns about privacy in Japan, despite a high level of support for science and technology. While 44% said they would agree to blood donation for a DNA bank, 28% were negative to donate, and another 28% answered they "don't know". The reasons behind these choices and the concepts of storage of genetic databases are partially reflected in the guidelines applied to collection of genetic databases, but greater and more independent community engagement will be important to increase public involvement in large scale genetics projects in Japan.

Genetic Databases

The Human Genome Project, the completion of which was declared in April 2003, was the international collaborative project to sequence the whole human genome of three billion base pairs. It was started in 1990 and took more than ten years to accomplish. Now in the "post-genome age", genetic projects are being conducted in a number of countries to explore human genetic variation. These large scale genetic research projects generally collect and analyze human genetic information together with health information, lifestyle information, and family information. In the case of Japan or the UK biobank this is from several hundred thousand people. This type of research also will continue for long time, not only retrospectively but also prospectively, because it is important to gather such kind of medical science research to substantiate the output from it by following donors for a sufficiently long time. To establish the tools to enable multidimensional investigation across the huge pool of genome information the research on SNPs (single nucleotide polymorphisms) and haplotype markers has been actively conducted. In some of those research projects, analyzed data, collected

samples including DNA, cell lines, blood and tissues are stored and maintained in databases, DNA banks, tissue banks or cell banks to develop useful research sources for future medical research.

Concurrently with the progress of human genome research various issues regarding ethical, legal and social implications (ELSI) have been pointed out. Various international bodies including UNESCO (United Nations Educational, Scientific and Cultural Organization), OECD (Organization for Economic Co-operation and Development) and HUGO (Human Genome Organization), have convened discussions on such issues from international or regional aspects, and many declarations, recommendations, and reports have been published. Although the ELSI research program itself has been controversial, it is a fact that it was very significant to contribute to accumulate numerous products of investigation and analysis, to provide information and educate the public including ordinary people and experts in multidisciplinary analysis, to develop human resources in ELSI fields (Clayton, 2003; Cambon-Thomsen, 2004). The wide type of information being gathered raises numerous privacy implications (Maekawa and Macer, 1999), and this paper examines some of these issues in a Japanese context. This paper also presents results of research on people's attitudes to donating genetic samples in Japan, including analysis of comments given, from a survey of the general public in 2003 (N=377). The paper reviews some of the laws and genetics research projects, and relates the concerns people expressed to the considerations made in community engagement for human genetics research.

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Public understanding regarding genetic research and ELSI issues

A random anonymous mail response survey was conducted over Japan in 2003 (Inaba and Macer, 2003). The results of the questions on donation of blood for genetic research and its storage in genetic databases are presented here. While Japanese people have shown to have certain extent of knowledge and understand about the genetic research and related ELSI issues in previous research, this survey obtained comments from 377 persons that reveal more of the reasoning that they have. There is a mix of different sectors of the Japanese public, education, different occupations (not shown), and rural and urban populations in each sample. We estimate sample error at +/- 5%. This type of analysis is useful for policy makers to know what are the real concerns of people, and help them to make policies based on the facts. This method focuses on descriptive bioethics, that is, how do people think about biotechnology (Macer, 1994).

There were few pessimists about science in general. Most people thought science does "more good" or the "same" as harm, and people who thought science does more harm has been a low number in past decade. The general images of science and technology Japanese people had were positive. However, when people were asked specific questions, their concerns were revealed, and respondents differentiated several applications of biotechnology (Inaba and Macer, 2004).

The first related question was regarding their willingness to donate for a genetic database, "Would you be willing to give blood from which DNA would be extracted to be put anonymously into a DNA bank so that researchers could study human genetic variation. This research would not personally help you because the sample is anonymous but would be useful for medical research in general." The answer could be selected from these options: "Yes" in general, "Yes" only for a temporary bank, "Yes" for permanent bank, "No", or "Don't know". 44% said "Yes" to blood donation for a DNA bank. 28% were negative to donate and another 28% answered they "don't know". One third of the "Yes" group allowed donating their blood only for temporary storage (Figure 1).

To analyze the reasons behind their attitudes towards blood donation for DNA bank, we classified their comments into 20 categories. Illustrative comments of the categories are given below. Those 20 categories could be grouped into 5 groups, for "the progress in science and medicine", "to help other people or public society", "if there are personal benefits", "conditionally" for example anonymous, only for public bank, necessary of personal notification, and "negative reasons". Figure 2 shows the number of comments in each group.

More than half of comments from the "Yes" group people were supportive for science and medicine. Also some particular comments for the "Yes" group were categorized into help others, especially among people who accepted to donate their sample for permanent or not specified DNA banks. Example comments are listed below (Y=yes, non-specified; t=temporary storage, p=permanent; N=no; DK=don't know).

Scientific research

Y(t) It's very significant for the research.

Y(t) Although I don't know about such research or DNA bank very well, if it will contribute for the research, I want to donate my blood.

Medicine

Y(t) It is significant for medical service and healthcare.

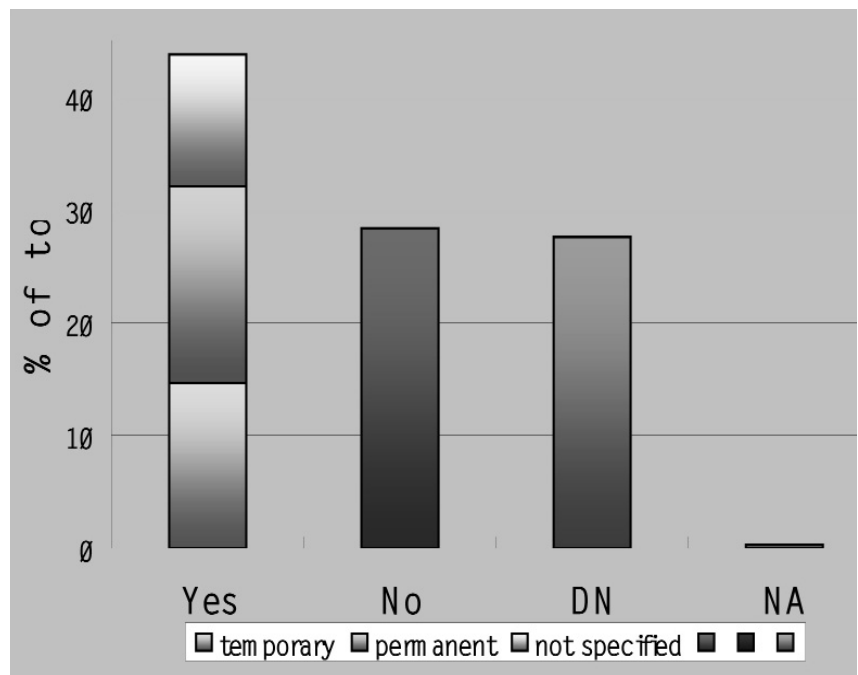


Figure 1: Japanese public attitudes toward blood donation for genetic research (N=377)

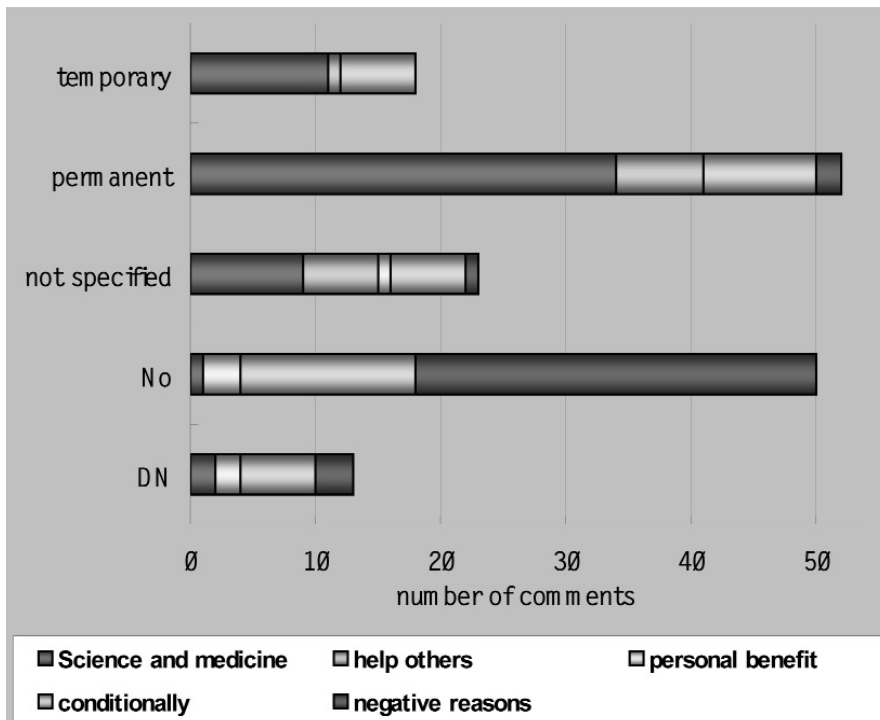


Figure 2: Reasons given regarding temporary, permanent or non-specified time period for storage of genetic data (N=377)

- 10 Anonymous important**
Y(t) I don't think there are any problems to donate samples for the bank. However, all samples must be anonymized.
Y If the sample is made anonymous in front of myself when I donate it, it is acceptable for me that my blood is utilized for the research.
- 11 If efficient it is useful**
Y(p) If it will be used efficiently, donation is acceptable for me.
Y If it is useful in future ages, it is acceptable for me to donate.
- 12 No problem**
Y(p) I don't care about donation of my blood.

Helping others

Y(p) If it will be helpful for someone else.

If strict conditions

Y(p) If the research group is sufficiently trustworthy, I can agree

with donation because it is meaningful.

N It is a trust problem. I can't trust.

Not to companies

Y(p) 7,2 If it will be used effectively, I will donate because I can understand it is necessary that the bank has sufficient number of samples. But I will donate on the premise of that the sample will go to the public institutes. I never donate my blood to any private companies. (+Scientific research)

Conditional

Y(t) If there is no possibility to do any harm to me, it is acceptable for me.

N I can't understand the necessity of it.

9 Insecure feeling if permanent

Y(t) I can donate my blood if it is just transient bank. I feel insecure about donating to a permanent one.

13 Personal benefit

Y I'm curious to know what kind of genes are making myself.

DK I'm in my 50s. I can't take any advantage from donation of my blood.

14 Personal experience

Y(p) I'm very keen to make contribution for the medical research. Actually now I'm donating my blood for the research. (The opinion from a patient with a genetic disease). (+Medicine).

N I am often asked to donate my blood because my blood type is Rh negative, that makes me more nervous to do so. If it is for my children or my neighborhood, maybe I can give my blood for them. (+Painful/burden)

15 Painful/burden

Y(p) I am willing to donate my blood if it is not so painful and I can be paid some money (if possible).

Y I think it is meaningful to contribute for the community if it is not so burdensome for individuals. (+Helping others)

N I'm fatigued by hard work too much, so I don't want to donate my blood. I don't like even usual blood donation, either.

16 Need personal notification

N This is an emotional issue for me. I don't like my genetic information to be utilized without any notification to me in somewhere I don't know.

DK If I will not be informed what kind of medical care the research will be useful for, or if the progress of the research will not be shown to me, I can't donate my blood.

17 Bad feeling

N I don't think I want to donate my blood.

N Now I can't help feeling scared (I can't make sure what kind of fear this is, though.), I probably will not donate my blood.

18 Fear of abuse

N Although I want to contribute for the research progress, I can't trust researchers totally. Even if it will be made anonymous, I can't help feeling scared thinking if it is abused, so I can't donate. (+Anonymous important)

N I feel scared what kind of research my blood will be used for. It is very horrific for me to imagine something like that a cloned human being of me might be born somewhere and be utilized as research material.

N I worry about that it might be abused.

19 Other negative reasons

N I don't want anything that came from me to remain.

20 Don't want

N I think the research is not necessary significant.

Some comments were cross-categorised (as indicated above). The comments that were categorized into "conditionally" could be found in all groups, but especially in the negative group, this category was the second most common. Concretely the sufficient security to protect privacy, sample anonymization, the examination of the appropriate purpose of the research, and the public nature were raised as essential points to be considered.

Many of the comments mentioned that since they couldn't understand about the research itself or the significance of the research, they couldn't decide easily to say, "Yes". There were several comments, which mentioned about personal benefit. The comments referring the blood samples or genetic information as "my own", "property" or "part of myself", were recognized. Some concrete wishes of ordinary people were found for example,

the results would be utilized for them, they would like to know their own genetic information, they would like to know the results, they would like to be informed what kind of research their samples were used, also interests to have certain compensation or direct benefit for donation, and they would like to receive the benefits from new science or technology. Among comments categorized into "negative reasons" people expressed just fear of abuse, a bad feeling to be utilized their own DNA for unknown research without any notification to them, distrust to researchers or private companies, or just donation was a burden.

The second question was about the consideration of anonymity versus the benefit to know individually useful genetic information. The question was "Would you prefer to learn any genetic information that might help you lower your risk of death, although the sample could not then be anonymous? Assuming researchers still protected your privacy." The result of this question was analyzed combined with the first question result (Figure 3). People who answered "Yes" toward donation for a DNA bank tended to show a positive attitude more frequently to know their genetic information if that is useful for their welfare, even if the sample later came to be not anonymous. While people who answered "No" to donation showed a more negative tendency to know the genetic information than the "Yes" group people regarding the DNA banking. From the comments they made for the previous question, it was speculated that they feel bad for their DNA to be utilized for research because of fear of harm or distrust towards science or researchers.

Evolution of the regulatory situation in Japan

In Japan the budget for ELSI research program was allocated in the initial stage of Human Genome Project, but after that less than 1% of the budget has been spent on ELSI purposes (Macer, 1992). Following the global trend, eventually guidelines for genome research that are relatively strict by international standards have been developed in 2001 in Japan, "Ethical Guidelines for Analytical Research on the Human Genome/Genes" (Ministry of Education, Culture, Sports, Science and Technology, 2001). However, compared with European countries or the United States or Canada, it is difficult to say the accumulation of basic research products and analyzed data to clarify the Japanese situation has been sufficiently developed in Japan. There are not so many products of ELSI research, including research papers, official papers

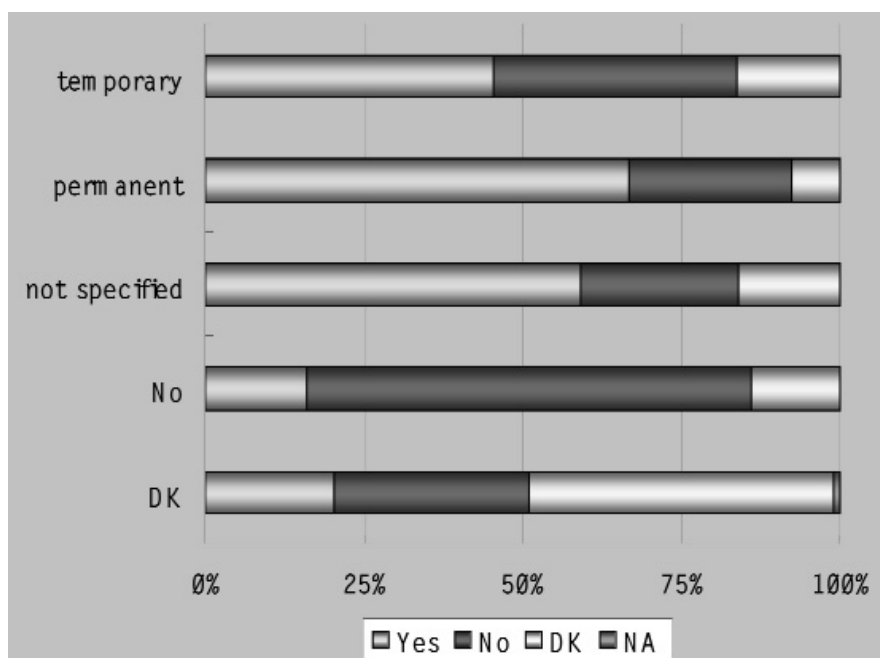


Figure 3: Japanese public attitudes toward anonymity in genetic research for temporary, permanent or non-specified time periods of storage of their genetic data (N=377)

and reports, or analyzed survey data that should be the most basic intellectual foundation for bioethics in the policymaking process, the development of human resources, or public education, for example.

The impetus for the 2001 guidelines came from UNESCO declarations. Following the global recognition of the significance to apply genome research findings for the treatment or diagnosis of diseases and the necessity to consider about the human dignity and human rights, the "Universal Declaration on the Human Genome and Human Rights" was adopted in 1997. It prescribes the general principles on the management of human genome in genetic research and its applications. Corresponding to the progress of the Human Genome Project, in light of projects on applied genome research and of the quality and quantity of information collected from the research subjects, UNESCO International Bioethics Committee (IBC) also developed a draft document, that the UNESCO General Conference adopted as the "International Declaration on Human Genetic Data" in 2003.

This declaration describes how human genetic data should be considered with certain attention because of its possibility to identify people's genetic predisposition of certain diseases or affect not only that person but also blood relations or the community to which they belong. Also it suggests concrete procedures to manage genetic samples and data regarding collection, treatment, utilization

and storage to respect human dignity, and to protect freedom and human rights.

Also from other international organizations several declarations, statements and guidelines regarding human genome, genetic research and its applications have been published. For example HUGO published the "Statement on the Principled Conduct of Genetic Research" in 1996, WHO made a draft "Proposal International Guidelines on Ethical Issues in Medical Genetics and Genetic Services" in 1998, and CIOMS published "International Ethical Guidelines for Biomedical Research Involving Human Subjects" in 2002. Although none of them has any legal binding force, they have affected the development process of interna-

tional or regional regulations in the world as global standards.

In Japan to accompany the Millennium Project for genetic research (2000-2004) fundamental ethical guidelines were established regarding the human genome, genetic research and its clinical uses following the global standards. In 2001, Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Health, Labour and Welfare (MHLW), and Ministry of Economy, Trade and Industry (METI) notified under the joint signatures of three ministries "Ethical Guidelines for Analytical Research on the Human Genome/Genes". It prescribes the concrete procedure for genetic research including the informed consent process, institutional review board (IRB) investigation on the research protocols, anonymization, sample management, and privacy protection purposing to protect human dignity and human rights.

Following that related guidelines on recent expanded genetic research to explore genetic information analyzing together with other information including health, environmental, or family information have been developed in the same period. In 2002, MEXT and MHLW delivered communally "Ethical Guidelines for Epidemiological Studies". MEXT and MHLW also published "Guidelines for Clinical Studies of Gene Therapy" in 2002. Also MHLW published "Ethical Guidelines for Clinical Studies" in 2003.

Importantly in Japan the legal framework to protect human privacy has been established and the legislation to protect personal information was enforced from April 2005 as the Act Concerning Protection of Personal Information. Although academic research activities are exempted from this law's application, to make such activities consistent with the new legal framework, the above-mentioned guidelines were reexamined in 2004 and also revised to adjust to the current situation. Medical research use of personal genetic and other information has been discussed in this process.

The Act Concerning Protection of Personal Information was issued on 30 May, 2003, with total enforcement on 1 April, 2005. The Act is composed of a set of three laws: (1) the 2003 Law No. 57 applies to all enterprises collecting, storing, or handling data of more than 5,000 persons, except national and local administrative bodies and independent administrative corporations (IAC) including national universities, national hospitals, and attached-to-national-university hospitals; (2) the 2003 Law No. 58 applies to administrative bodies; and (3) the 2003 Law No. 59 applies to the IAC ([Act concerning Protection of Personal Information (Japan Law No. 57, issued on 30 May 2003)].

Enterprises collecting/storing/handling data of fewer than 5,000 persons or individuals using personal data not for business purposes are exempt from the Act. The main purpose of the Act is to state the basic concepts and basic policies regarding the proper handling and protection of personal information, the protection of the rights and interests of individuals, the governmental duties in relation therewith, and at the same time the appropriate utilization of personal information. Its essential framework is based on the recommendation and the eight principles governing the Protection of Privacy and Transborder Flows of Personal Data in 1980 by the Council of the Organisation for Economic Co-operation and Development (OECD), which aimed to harmonize privacy protection and prevention of economic interruptions in international flows of data. Therefore, the enterprises concerned are basically obliged: (1) to specify the purposes of personal data utilization, (2) not to use that data beyond these specified purposes without obtaining the consent of the data subject, (3) not to transfer that data without her consent, (4) not to collect personal data in a wrong or fraudulent way, (5) to keep that data accurate and up-to-date, (6) to take necessary measures for safeguarding that data, (7) to monitor their data handling personnel and consignees, (8) to secure confidentiality of that data, (9) to open the purposes of that data utiliza-

tion to the data subject or to the public, (10) to make the names of the enterprises and the purposes of that data utilization readily available, (11) to disclose or correct the data relating to the data subject at her request, (12) to suspend the utilization of that data at her request because of the misconduct regarding (2) or (3), and (13) to deal with complaints regarding personal data which they have.

Human genetic variation research projects in Japan

In Japan large-scale genetic epidemiology projects were enthusiastically started from the end of 1990s. Especially national projects, they were aiming not only research achievements, but also building infrastructures including technological development, facility enhancement, and research resources establishment to empower Japanese life science field in the genomic era. Also it was expected to build up collaborative structures for human genome research or epidemiological research in Japan to coordinate industry, government and academia including universities, hospitals, institutes, and related industries.

One of the main early national initiative projects was the Millennium Project (2000-2004), life science and technology was one of the three main focus fields of this project. As part of the project, human genome research programs including functional analysis of human genome, SNP (single nucleotide polymorphisms) analysis, genetic studies focusing on the main five lifestyle-related diseases or drug response, and building databases of the products were funded. This project also included consideration for ELSI issues including building the framework to ensure security for individual information and privacy, and public understanding on such research and its applications. Concretely it established rules and guidelines simultaneously in the project.

Focusing on pharmacogenetics, pharmacogenomics and personalized medicine based on genome research products, 43 Japanese pharmaceutical industries conducted the Pharma-SNP Consortium (PSC) project (2000-2003). They collected blood samples from 1000 healthy Japanese, established cell lines, and analyzed DNA extracted from them. Health, environmental and family information was collected from donors also. They studied on genes related to drug metabolism or transportation to explore genetic variations that affect on drug response of Japanese. The analyzed data and cell lines have been made public after making them anonymized. They also aimed to

establish the model including informed consent process, management of data and samples, and anonymizing methodology to conduct such kind of research involving human subjects following both Japanese and global regulatory standards. Through the Millennium Project and PSC project, standard model for informed consent process, anonymization, privacy protection, and samples management have been developed and educated to regarding people.

Now in post Millennium Project age, based on the scientific achievements and progressed infrastructures, various genetic research programs are being more enthusiastically and extensively conducted both in academic and industrial areas. The globalization and international competition of the research in this field is being advanced also. The BioBank Japan Project was initiated as MEXT funded five years project (almost 200 million dollars) from June 2003. In the project DNA and serum samples from 300,000 patients of 46 different multifactor diseases, various factors including genetic and environmental backgrounds are involved in the establishment of them, are aimed to be collected and stored in the biobank to develop the significant research infrastructure (<http://www.src.riken.go.jp/eng/src/project/person.html>). Various kinds of information including health, environment, and family details are being collected also. Using these samples and information, the mechanism of the disease establishment and drug response will be analyzed. Since November 2004, when the project had collected samples from almost 80,000 patients, they started to distribute collected samples for other research use under the investigations approved by associated IRBs from the beginning of January 2005.

The Haplotype Mapping (HapMap) Project is an international collaborative project to determine the common patterns of DNA sequence variation across the human genome by genotyping four populations in the world including Japanese, Han Chinese, Northern and Western European ancestry (CEPH) and Yoruban ancestry. This project is positioned as post Human Genome Project, and the products of it have been enthusiastically expected to empower the progress in life science research in "post-genome age". The database including developed map and the cell bank of collected samples is freely available in the public domain to be utilized for future genetic research by researchers in the world. The project was initiated by the International HapMap Consortium consisted of organizations and institutions of five countries, USA, Japan, United Kingdom, Canada and China from October 2002.

Japanese government MEXT is supporting almost 25 % of total budget for the project, and University of Tokyo, Institute of Medical Science and RIKEN SNP Research Center are genotyping almost 25% of total genome also.

The International HapMap Consortium consists following working groups for; genotyping centers, community engagement/public consultation and sample-collection groups, analysis groups, Ethical, Legal and Social Issues, SNP discovery, scientific management, and initial planning groups. Prior to the activity of Japanese community engagement/public consultation and sample-collection group in which the authors worked as two of four members, this opinion survey was conducted (International HapMap Consortium, 2004).

Discussion

In the public survey results towards their donation for a genetic database, the Japanese population was split into three major groups, "Yes", "No" and "Don't know" without significant difference. Respondents (one-fifth of those requested to answer the anonymous mail response survey) had some knowledge of "genetic research", "informed consent" and "privacy protection", and it seemed that the resources of their knowledge were mainly due to their own direct and indirect experiences, newspapers and TV programs. Irrespective of their willingness for donation, both positive expectations and concerns toward science and medicine, and both trust and distrust to research and researchers were found among the comments people made. As illustrated by the comments, some people showed willingness to contribute to science or help others, and also fears about causing discrimination or abuse simultaneously. But whether showing willingness or fear, there were few deep considerations regarding the meaning of participation to genetic study, progress of medicine, effects on community and relationship between citizen and society.

In follow-up public meetings, some common issues discussed currently globally from the ELSI perspective regarding the biobank projects were also found among their comments, including issues of genetic information and biological materials as the property of the donating individuals or community (Japan), patent issues, benefit sharing issues and informed consent for conditional use in future research.

Considering that the stored samples in the banks will used for other research applications than those the initial samples have been donated for, to describe the research utilizations in specific man-

ner is getting impractical, although it is required regarding the informed consent procedures in current norms or guidelines. In this case, it is also difficult to understand about possible risks caused by future research use for donor candidates in the informed consent process. Under such changing circumstances, certain reviews on traditional informed consent procedure might be necessary (Kegley, 2004). In the HapMap project, the willingness to be notified regarding the research use of donated samples was observed among not a few lay people in Japan. People showed their interests to know the detail of researched donated samples will be used for, the progress of them, and even the scientific or profitable results.

To build the reliable framework for the public in the genetic research project, community engagement is important, and in this process it is necessary to involve a range of ordinary citizens including both donors and non-donors. It is difficult to consult really ordinary people in community engagement, not only the activists having very negative or positive voices and used to make remarks. Citizens' groups may also be useful, but there are few in Japan. Still a survey itself is not sufficient to engage public opinion to gain valuable input for policy development.

Building well balanced knowledge and deep considerations among the public is expected to develop the awareness of the issues regarding genetic research among ordinary people, and persons having such awareness will be able to join to the discussion across people with multidisciplinary backgrounds. The citizens who are not activists may not be used to make remarks but have capabilities to dialogue from a citizen's standpoint across multidisciplinary people based on well-balanced knowledge, not only on technical matters but also ethics, regulations, and social issues, may be expected to be involved in the community engagement.

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