Letter to the Editor

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Han Chinese Cell and Genome Bank in Taiwan: Purpose, Design and Ethical Considerations

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From October 1, 2002 to January 14, 2004, the Institute of Biomedical Sciences, Academia Sinica, Taiwan, conducted field work involving interviewing and recruiting 3,380 Han Chinese in order to establish a Han Chinese Cell and Genome Bank in Taiwan. The aims of this undertaking were several fold: (1) to collect representative genetic material for population genetic research, particularly for use as controls in disease association studies in Chinese people, (2) to document the genetic diversity of Han Chinese in Taiwan at the beginning of the 21st century, and (3) to create a bank of material that will prevent the repetitive collection of genetic material from the general public by the academic and medical community.

The National Science Council (NSC) in Taiwan has launched the 'National Research Program for Genomic Medicine (NRPGM)' in 2002 as the first phase of Taiwan's Biotechnology Initiative in response to the deciphering of the human genome in 2000. The goal is to develop Taiwan's competitive edge in medical research particularly for prognosis, diagnosis, and treatment of Taiwanese important genetic diseases. The Han Chinese cell and Genome Bank project was jointly supported by NRPGM and Academia Sinica. Comprehensive cores have been established in NRPGM to complement relevant studies. The National Clinical Core and National High-throughput Genotyping Core, funded by NSC and directed by the Institute of Biomedical Sciences, Academia Sinica, Taiwan, played major roles in carrying out field work and in the genotyping of the genetic material. A policy and mechanisms for the release of DNA information have been established for genetic research communities in Taiwan and abroad.

In order to obtain a representative sample of genetic material for the bank; a stratified, 3-staged, probability clustering sampling scheme (see appendix, table 1, and fig. 1) was adopted. Sampling was designed to have around 278 male and 278 female subjects respectively in each of the 6 age groups (20–, 30–, 40–, 50–, 60–, 70–) so that there would be sufficient numbers of sex/age matched controls for a range of diseases. Of the people living in the registered households that were contacted, a total of 73.4% took part in the study.

Plasma, DNA, and lymphocytes were collected and banked, and measurements including basic blood chemistry, blood pressure, peak flow, and anthropometric parameters were taken (see table 2). A questionnaire (table 2) on ethnicity, disease history and medication, life styles, and cognitive function of the elderly was administered by trained nurses in a door-to-door survey, following a standardized protocol. Complete questionnaire and bio-specimen data were available for 3,380 people. This information can be used to define phenotypes for association study and to select controls. The EBV-transformed lymphoblastoid cell lines had been established by the Bioresource Collection and Research Center, Hsinchu, Taiwan.

Table 1. Sampling scheme and sample size

Strata	Geographical areas	Towns or city districts selected in each stratum	Villages or city blocks selected in Each district	Projected persons in each village or city block	Projected sampled persons in each stratum	Actual sampled persons in each stratum
1	North	8	24	42	1,008	1,040
2	Northwest	6	18	25	450	460
3	Mid-west	6	18	35	630	626
4	Southwest	6	18	31	558	553
5	South	6	18	30	540	543
6	Northeast	2	6	25	150	158
Total		34	102		3,336	3,380

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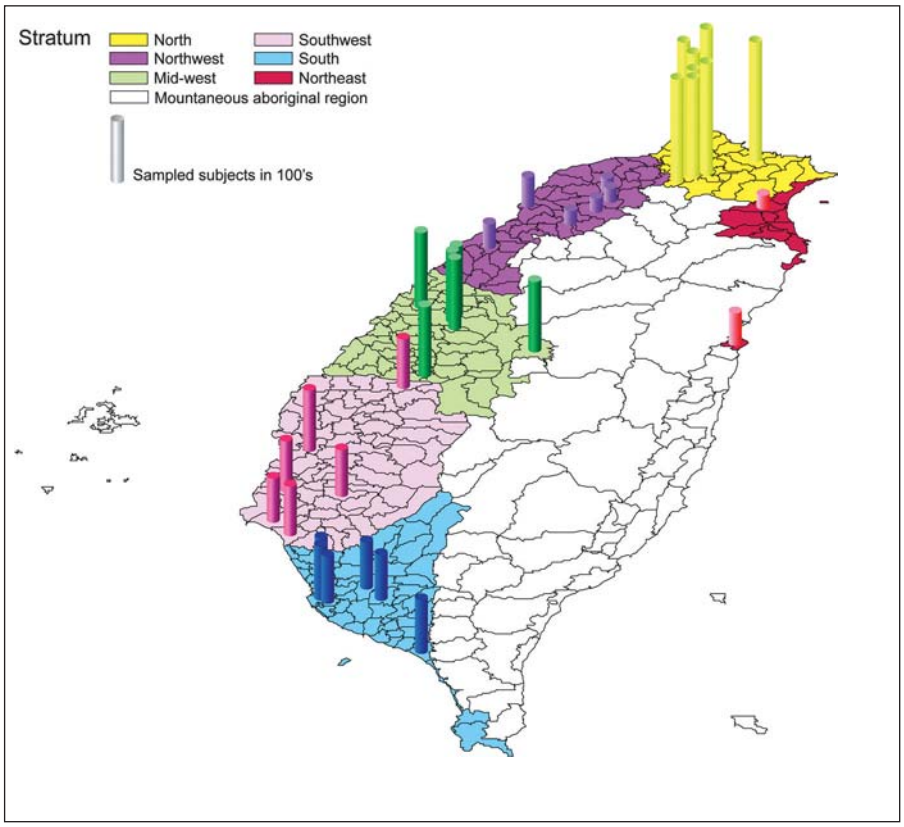

Fig. 1. Geographic distribution of the participants in the Taiwanese Han Chinese Cell and Genome Bank.

Table 2. Phenotype information collected

Questionnaire information	Physical exam items	Clinical chemistry
Birthday	Blood pressure	Cholesterol
Gender	Pulse rate	HDL-C
Education	Body weight	Uric Acid
Ancestral ethnic origin of the parents and the grandparents	Body height	Electrolytes (Na^+, Cl^-)
Medical history	Waist circumference	BUN
Familial disease history	Hip circumference	Creatinine
Medication history for the past six months	Peak flow rate	SGOT
Life style (smoking, alcohol consumption, and betel nut chewing)		SGPT
Short Portable Mental Status for the elderly		HbA1C
		Antibody for hepatitis C
		Antibody for hepatitis B-surface antigen
		Antibody for hepatitis B-core protein

Since a small proportion (2%) of the Taiwanese population is of aboriginal descent, questions regarding the ancestral origin of parents and grand-parents were used to exclude people with significant aboriginal ancestry. The Han Chinese in the study consisted of three major groups: Minnan (67.4%), descendants of migrants to Taiwan over the past four hundred years from the Fukien province of China; Hakka (11.2%), descendants of migrants over a similar time period from the Canton province; and mainlanders (6.7%), representing new arrivals over the last century from all other provinces of China. The remaining 14.7% were primarily a mixed population of the three groups. Our preliminary data on the SNP profiles in the major histocompatibility complex (MHC) region (6p21.3) showed no significant difference among these groups [1], but obvious disparity between Chinese and Caucasians.

Taiwan has a well-established government infrastructure that oversees the scientific, legal, and ethical aspects of clinical trials. However, regulations about genetic research and genetic material storage were still in their infancy in 2002, when the Department of Health published the first guidelines on human sample collection, mainly based on the Helsinki Declaration, version 5. In order to meet higher ethical standards in this landmark study in Taiwan, the Internal Review Board (IRB) of the Institute of Biomedical Sciences, Academia Sinica – precursor of the Medical Ethics Committee, Academia Sinica [2] – provided major input regarding the ethical considerations of this project. In the consent form, which accords well with the DOH guidelines and Helsinki Declaration, version 5, we explicitly explained to the participants (a) the purposes of this Cell and Genome Bank, (b) their actual involvement in terms of donating blood samples and revealing personal information, (c) risks and benefits of their participation, (d) privacy protection measures, (e) the meaning of cell lines, (f) potential use of the samples for multiple diseases and by a third party (including research and commercial organizations), (g) profit policy, and (h) procedure for withdrawal [3].

We could not specify the full range of diseases that the samples will be used as controls for in the future. This may raise ethical concerns that participants have given 'blanket' consent. Such concerns may be aggravated by the stringent privacy protection measure that was adopted by this Cell and Genome Bank at the request of our IRB: namely, that all personal identifiers must be destroyed within a year after completion of the field work. This process, which was clearly explained in the consent form, makes it impossible for participants to withdraw after the removal of identifiers, or to disallow their samples to be used by any particular research that they find ethically objectionable. The participants may therefore be thought to be deprived of an effective means of securing control over future research. However, to safeguard the interests of participants, the Institute of Biomedical Sciences has established a user committee to evaluate the objectives of projects applying for access to the repository. This committee consists of two investigators of the project, one medical doctors, one ELSI expert, and one lay representative of general publics. Transfer of DNA samples to external researchers must be accompanied by signed agreements, and transfer from one researcher to another without the user committee's approval is strictly prohibited. Release of control DNA materials from this bank will be divided into several stages. A panel of 94 individuals is made available at the present time. More panels will be made available in the near future. Study description, details of DNA release policy, and application procedure and forms can be found in the following website: http://ncc.sinica.edu.tw/han-chinese_genomebank/

We appealed to altruistic motivations in the people who were randomly selected for recruitment. Not only must participants waive their right to withdraw beyond a given period of time, but they must also waive any share of intellectual property rights to Academia Sinica for results of research utilizing their samples. The fact that recruitment for the Cell and Genome Bank proceeded smoothly under these terms may serve to indicate a significant degree of receptiveness of Taiwanese people to the idea of contributing to a biobanking project that aims at the common good, provided their privacy is well protected. Altruism among ordinary citizens in Taiwan is still prevalent nowadays: a recent, as yet unpublished finding by the Center for Survey Research at Academia Sinica shows that out of 1,089 people interviewed in a nationwide survey conducted in 2005, 76.7% stated that they would be inclined to donate blood samples to a government-funded biobanking project if privacy protection is assured, and 51.3% would still do so when they were told that leakage of personal genetic information may be a concern.

Undeniably, part of the reason why we had little difficulty in recruiting participants among the general public stems from the prestigious status enjoyed by Academia Sinica as the highest-ranking institution for basic research in Taiwan. We have continued to maintain the public's trust. One of the major purposes of this Cell and Genome Bank is to facilitate genetic research in order to find novel genetic variants for important diseases of Chinese people. Recent studies on Stevens-Johnson syndrome [4] and on severe cutaneous adverse reactions caused by allopurinol [5] are good illustrations of how genetic materials from this genome bank can be used to locate genetic variants associated with diseases. Unraveling genetic determinants of these diseases can lead to prevention and new treatment, and to improvement of the national healthcare services in Taiwan.

While this Han Chinese Cell and Genome Bank will, hopefully, prove to be a powerful resource for studying genetic variation and disease association, we have tried to ensure its compliance with normative requirements. We do not think, however, that the ethical principles adopted for the establishment and future usage of this repository have made us immune from criticisms. The publicity and challenges we received in the process have stimulated and sustained open discussion, urgently needed in a burgeoning democracy like ours, over the difficult and complicated issue of how to put in place a trustworthy regulatory framework for genomic research in Taiwan, where ethical issues and social impacts have particular cultural idiosyncrasies. We hope that our initiative provides an important experience not only for Taiwan, but also for other countries, especially those in Asia.

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Appendix

Sampling Scheme

A stratified, 3-staged, probability clustering sampling scheme (see table 1) was designed in collaboration with the Center for Survey Research, Academia Sinica. A total of 329 non-aboriginal townships or city districts as primary sampling units (PSU) were grouped into 6 strata: north, northwest, mid-west, southwest, south, and northeast. The 6 strata were taken from the areas other than the central mountain range, which is predominantly inhabited by Taiwanese aborigines. 2–8 PSUs were drawn from each stratum (stage 1), proportional to its size. Then, 6–24 villages or city blocks were selected within each PSU again proportional to the village size

(stage 2). Within each village (stage 3), we selected 25– 42 people aged 20 and older, drawn as a cluster from the list provided by the Taiwanese Household Registry. The sampling was designed to collect around 278 male and female subjects respectively in each of the 6 age groups (20–, 30–, 40–, 50–, 60–, 70–) so that there would be sufficient numbers of sex/age matched controls for a range of diseases. The geographical distribution pattern is shown in figure 1.

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