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ORIGINAL ARTICLE

Nationwide survey on predictive genetic testing for late-onset, incurable neurological diseases in Japan

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Abstract A nationwide survey was conducted for predictive genetic testing for late-onset, incurable neurological diseases. A questionnaire was sent to 125 university hospitals and national hospitals, and was returned by 69% of them. Of the 86 responding hospitals, 63 had genetic counseling clinics and answered the questions concerning predictive testing. Of these, 46 had experienced clients with an interest in or a request for predictive testing during the period from April 2004 to March 2006. A total of 322 clients were accumulated, the majority of which were interested in myotonic dystrophy (n = 150), followed by spinocerebellar ataxia (n = 86), spinal and bulbar muscular atrophy (n = 40) and Huntington's disease (n = 31). Most such clients were counseled by medical doctors, who had the "Japanese Board of Medical Genetics, Clinical Geneticist" certification, but others, including neurologists, nurses, clinical psychologists or genetic counselors also contributed, albeit to a lesser extent, to genetic counseling in Japan. Many respondents felt that a multidisciplinary approach by a counseling team consisting of a clinical geneticist, a neurologist, a genetic nurse, a clinical psychologist and a genetic counselor had not yet been established. There will be a great need for educated and trained non-medical doctor staff not only to improve the quality of genetic counseling and psychological support for such clients, but also to conduct the psychosocial research on Japanese clients requesting predictive genetic testing.

Keywords Genetic counseling · Predictive genetic testing · Neurological disease · Clinical geneticist

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Introduction

In Japan, genetic counseling has not yet taken root as a common clinical practice, but genetic testing and genetic research for human diseases have become increasingly popular. Along with this trend, the establishment of a genetic counseling system is strongly needed to successfully conduct clinical practice and research for genetic diseases. In recent years, specific genetic counseling departments have been set up nationwide. Now more than 60 hospitals have opened genetic counseling clinics in Japan. The National Liaison Meeting for Clinical Sections of Medical Genetics has been held annually since 2003, where the persons responsible for genetic counseling departments have gathered from throughout the country and held discussions on several issues concerning the genetic counseling system in Japan.

The most controversial topic in clinical genetics is how we should handle the need for predictive and prenatal genetic testing, especially, predictive testing for late-onset, incurable neurological diseases such as Huntington's disease (HD) and spinocerebellar ataxia (SCA). It raises various ethical, legal and psychosocial implications (Brandt

1994; Evers-Kiebooms and Decruyenaere 1998; Chapman 2002; Taylor 2004); thus, pre-test genetic counseling and post-test follow-up should be carefully conducted for clients.

Predictive testing for late-onset, incurable neurological diseases has become popular in the United States, Canada, Australia and various European countries, and integrated guidelines and protocols for predictive testing have been established in these countries (Craufurd et al. 1992; Quaid 1992; International Huntington Association (IHA) and World Federation of Neurology (WFN) 1994; Benjamin et al. 1994; Decruyenaere et al. 1995; Mandich et al. 1998; Robins Wahlin et al. 2000). However, little is known about the actual circumstances surrounding this issue in Japan, and only a few studies on psychological aspects of clients seeking predictive testing have been published (Abe and Itoyama 1997; Muto 1998; Yoshida et al. 2002).

In this survey, we investigated the current situations and attitudes of genetic counseling departments in Japan concerning predictive testing for late-onset, incurable neurological diseases.

Procedure

We sent the questionnaire to 125 institutions (university hospitals and national hospitals) in Japan, most of which were highly advanced and specialized medical center hospitals under the supervision of the Ministry of Health, Labor and Welfare, to investigate the actual circumstances concerning predictive testing for late-onset, incurable neurological diseases. The diseases we indicated in the questionnaire included HD, SCA, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), spinal and bulbar muscular atrophy (SBMA), myotonic dystrophy (DM1) and prion disease. Familial amyloid polyneuropathy (FAP) was also included, although it may no longer be incurable due to liver transplantation. Before submitting the questionnaire, we asked whether or not the hospital had a specific genetic counseling department. If not, the responding persons were instructed not to answer the questions about predictive testing. The questionnaire contained five questions as shown in Table 1. The chief person responsible for the genetic counseling department in each hospital was asked to fill out the questionnaire. In this paper, a clinical geneticist indicates a medical doctor who has the "Japanese Board of Medical Genetics, Clinical Geneticist" certification, and a genetic counselor indicates a non-medical doctor who has the "Japanese Board of Medical Genetics, Certified Genetic Counselor" certification. The certificates are given by the Japan Society of Human Genetics and the Japanese Society for Genetic Counseling.

Results

The questionnaire was returned by 69% ($n = 86$) of the hospitals surveyed. Of the 86 responding hospitals, 63 (73%) had clinics that specialized in genetic counseling and answered the questions concerning predictive testing as shown in Table 1. The distribution of these 63 hospitals is shown in Fig. 1. The remaining 23 hospitals did not have genetic counseling clinics. Of the 63 hospitals with clinics, 46 (73%) had clients with an interest in or a request for predictive testing for late-onset, incurable neurological diseases during the period from April 2004 to March 2006. Of these 46 hospitals, 30 (65%) were attached to national universities or national centers, 13 (28%) were private universities, and 3 (7%) were public universities. The remaining 17 hospitals had no requests or inquiries for predictive genetic testing during this period.

In total, 322 clients from 243 families (excluding FAP) were reported from the 46 responding hospitals (Table 1 Q2). National and public hospitals (total 33) had 194 clients, and private hospitals (total 13) had 128 clients. The maximum number of clients was 80 in a hospital located in the Kanto area. Eleven hospitals had more than 10 clients, and 27 had less than 5 clients during this period. The greatest interest was shown in DM1 (150 clients, 47%), followed by SCA (86 clients, 27%), SBMA (40 clients, 12%) and HD (31 clients, 10%). These clients were distributed nationwide, and more than ten of the hospitals had clients interested in each of the following four diseases (DM1: 31 hospitals; SCA: 30; SBMA: 10; HD: 14). Those interested in prion disease (13 clients, 4%) were much fewer and were found in only three hospitals; a single hospital reported 10 of the 13 clients for prion disease. The interest in ALS was very small (2 clients, <1%) and was found in only two hospitals. There were no clients reported to be interested in AD during this period. There was a significant number of clients (more than 13 clients from 11 families) interested in FAP, but the exact number was not obtained because the answer "a lot" was returned from a single hospital. In contrast to the clients for DM1 or SCA, those for FAP were exclusively concentrated in two hospitals that are close to the former endemic areas for this disease and that have actively conducted liver transplantations for the patients.

The professions of the participants in genetic counseling sessions are summarized in Table 1 (Q3). Clinical geneticists participated in 75–100% of the total counseling sessions in 35 of the hospitals (56%). The contributions of neurologists and nurses were much smaller; they participated in 75–100% of counseling sessions in just 14 and 13 hospitals, respectively. The participation of the other professions (psychiatrists, clinical psychologists, genetic counselors, etc.) was not common. Seventeen

Table 1 Questionnaire and results

Q1	**Have you had clients who visited your hospital with an interest in or a request for predictive genetic testing for late-onset, incurable neurological diseases during the period from April 2004 to March 2006? (total responding = 63)**					
	Yes; (go to Q2-5)	46				
	No; (go to Q4-5)	17				
Q2	**What kinds of diseases were your clients interested in? Please indicate the numbers of families (clients) for each disease. (total responding = 46)**					
	Myotonic dystrophy	110 (150)				
	Spinocerebellar ataxia	68 (86)				
	Spinal and bulbar muscular atrophy	32 (40)				
	Huntington's disease	26 (31)				
	Prion disease	5 (13)				
	Amyotrophic lateral sclerosis	2 (2)				
Q3	**How much did the following professions contribute to the counseling sessions of such clients? Please select the most appropriate percentage among the following: a: 0%, b: 0-25%, c: 25-50%, d: 50-75%, and e: 75-100% ('0%' indicates no participation and '100%' indicates full-time participation in the counseling sessions.)**					
		0%	**0-25%**	**25-50%**	**50-75%**	**75-100%**
	Clinical geneticist (46)#	2	1	4	4	35
	Neurologist (41)	10	7	7	3	14
	Psychiatrist (33)	26	3	3	0	1
	Nurse (40)	13	5	6	3	13
	Clinical psychologist (37)	17	6	6	0	8
	Genetic counselor (28)	26	0	0	1	1
Q4	**If such clients visit your department in the future, how will you handle them? Please select the most appropriate answer from the following: (total responding = 63)**					
	You will provide genetic counseling in your own department	36				
	You will refer the client to another hospital without providing genetic counseling yourself	2				
	You will make your decision (1 or 2 shown above) depending on the situation and/or disease of interest of the client	23				
	You will reject the client	0				
	Not answered	2				
Q5	**What do you think are the most important requirements for maintaining genetic counseling for such clients? Please select the three most important requirements from the following and rank them in the order of their importance, (1st) being most important. (total responding = 63)**					
		1st	**2nd**	**3rd**		
	Genetic counseling staff	33	12	7		
	Time and space for clinical practice of genetic counseling	5	21	6		
	Administrative support for genetic counseling	10	8	8		
	Genetic testing system	5	9	17		
	Cooperation with the other hospitals	1	7	12		
	Understanding and recognition of clinical genetics by the general	8	3	7		
	Others	1	3	6		

#Numbers in parentheses indicate those of responding hospitals

hospitals where nurses and/or clinical psychologists participated in 75–100% of counseling sessions had 201 clients (62%), while 20 hospitals where both of these professions participated in only 0–25% had 60 clients (19%).

Concerning the attitudes toward such clients in the future (Table 1 Q4), 97% of the responding hospitals ($n = 61$) showed positive attitudes toward these clients. Thirty-six hospitals (57%) indicated that they would conduct genetic counseling in their own hospitals. Two (3%) would refer the

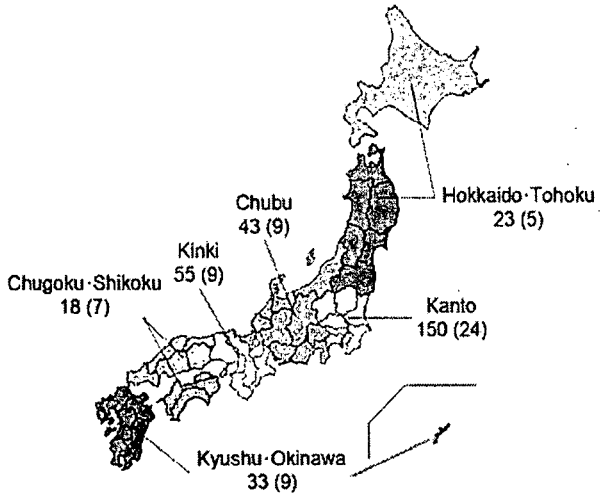

Fig. 1 The distribution and numbers of clients and responding hospitals. The numbers of clients shown here indicate the sum of those with an interest in or request for predictive testing for DM1, SCA, SBMA, HD, prion disease and ALS, but not for FAP. The numbers of responding hospitals in each district are indicated in the parentheses

clients to other hospitals without counseling them themselves, and 23 (37%) would make these decisions based on the individual clients.

We inquired about the needs of persons involved in the genetic counseling of such clients (Table 1 Q5). The most important requirement was an improvement in the counseling staff, followed by improvements in the environment of clinical practice for genetic counseling and the establishment of genetic testing systems. Administrative or financial support for genetic counseling and cooperation with other hospitals in genetic counseling were also strongly needed.

Discussion

The number of genetic counseling departments in hospitals has been increasing in Japan in recent years. This was the first nationwide survey of such departments conducted concerning predictive testing for late-onset, incurable neurological diseases. Inherent in such procedures are several ethical and social issues (Brandt 1994; Evers-Kiebooms and Decruyenaere 1998; Chapman 2002; Taylor 2004), and little information on the present conditions surrounding this issue has been accumulated in Japan (Abe and Itoyama 1997; Muto 1998; Yoshida et al. 2002).

It is obvious that a significant number of the clients with an interest in or a request for predictive testing for late-onset, incurable neurological diseases visited hospitals over last 2 years. The clients were not concentrated in specific districts of Japan, but were distributed nationwide. We should keep in mind that the numbers of clients reported in this paper may represent an underestimate, because not all hospitals and clinics were surveyed. Even in the hospitals we did survey, some respondents indicated that neurology departments in their hospitals have such clients independently from genetic counseling departments. Considering that several delicate and complicated issues are involved with predictive testing for the diseases under study, however, it is likely that the clients have concentrated in the hospitals that have specialized genetic counseling clinics. Thus, we presume that the numbers of clients in this paper roughly reflect the current situations on this matter.

There was a marked difference in the number of clients among hospitals we surveyed. The number of clients may be influenced by several factors. They include the locations of hospitals, the attitudes of counseling staff, the activities of genetic counseling departments and cooperation and specialties of neurologists involved. Academic interest of the neurology department in the university may also be closely associated with the numbers and kinds of diseases of the clients. A representative example for this is seen for FAP, as shown in Results. Of 11 hospitals that had more than 10 clients during the period of interest, nurses and/or clinical psychologists participated 75–100% of the time in genetic counseling sessions in 7 hospitals, whereas, neither of them participated at all in 2 hospitals. As far as predictive testing for late-onset, incurable, neurological diseases, therefore, the participation of non-medical doctor (non-MD) staff in the counseling session does not seem to directly parallel the number of clients. But we can say that requests of clients for predictive testing might be a driving force for having nurses or clinical psychologists involved in genetic counseling sessions. The type of hospitals (national, public or private) had no effect on the number of clients.

It is reasonable that the number of clients interested in DM1 was much greater than those interested in either HD or SCA. The major reason for this is that predictive testing for DM1 often may be linked with reproductive decision making, based on the fact that prenatal genetic testing for DM1 has often been performed in Japan. Many clinical geneticists and neurologists also feel that the matter of predictive testing for DM1 is far different than for HD or SCA because DM1 can be diagnosed by clinical and laboratory findings other than genetic testing, even when a person is not aware of the symptoms. Thus, a significant portion of DM1 clients who were likely to test negative may have already had genetic testing in Japan. This may also be the case for SBMA, because SBMA can be detected by electromyography at the preclinical stage. Thus, careful consideration should be given to whether different predictive testing procedures should be applied to DM1 or SBMA than to HD, SCA or AD.

During the period of the survey, clinical geneticists were predominantly involved in genetic counseling sessions for the diseases under study, probably regardless of their own medical specialties. By contrast, the contribution of neurologists was far less than that of clinical geneticists in Japan. Some respondents strongly desired an active participation of neurologists in the counseling team. Neurologists who are involved in genetic testing for patients with hereditary neurological diseases should give much more consideration to the possibility of predictive testing of the patients' family members. The involvement of non-MD staff such as nurses and clinical psychologists was not common in Japan. These results indicate that genetic counseling has been still largely dependent on medical doctors with an interest in clinical genetics and a multidisciplinary approach by a genetic counseling team has not yet functioned effectively in Japan. This situation is mainly because it is very difficult for non-MD staff (nurses, clinical psychologists, genetic counselors) to secure a position for genetic counseling in the hospital in Japan. Especially clinical psychologists, if involved in the genetic counseling team, have been compelled to work under limited conditions. From the viewpoint of hospital management, the cost-benefit performance is poor for genetic counseling, and non-MD staff specific for genetic counseling cannot be employed. In this study, some respondents desired a hospital cost system that profited from genetic counseling.

To improve the present conditions, we first need to have genetic counseling widely recognized in the general population. Then we need to know in more detail how satisfied clients are with genetic counseling sessions and to know what benefit they receive from having non-MD staff in the genetic counseling sessions. A counseling team consisting of a clinical geneticist, a neurologist, a genetic nurse and a clinical psychologist for each session is generally advisable. We believe this format is desired for patient or client-centered genetic counseling. The education and training of non-MD staff will be of great help not only to maintain the quality of genetic counseling for clients, but also to conduct medical research on the psychosocial aspects of genetic counseling in Japan.

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Long-term Follow-up of Patients with Multiple Endocrine Neoplasia Type 1

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Abstract. Whether early surgical treatment of non-functioning pancreas islet cell tumor (NFPT) provides a favorable quality of life and life expectancy in patients with multiple endocrine neoplasia type 1 (MEN1) remains controversial. We analyzed the long-term clinical courses and surgical outcomes of 14 Japanese patients with MEN1-associated NFPTs. NFPTs smaller than 20 mm in diameter did not show any apparent growth over a long monitoring period. Furthermore, these small NFPTs did not metastasize to regional lymph nodes or the liver. On the other hand, the development of additional NFPTs or metastasis was found in five of six patients with large (35 mm or larger) NFPTs. Among the seven patients who underwent a partial pancreatectomy, six patients developed impaired glucose tolerance or diabetes. The accumulation of more prospective data is needed to clarify the optimal surgical indications for patients with NFPTs, especially among the Japanese population, which has a relatively low insulin secretion potency compared with non-Hispanic white and African-American populations.

Key words: MEN1, Tumor growth, Surgical indication, Pancreatectomy, Diabetes

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MULTIPLE endocrine neoplasia type 1 (MEN1) is a relatively rare autosomal dominantly inherited disorder characterized by hyperplastic and neoplastic disorders of endocrine organs, such as the parathyroid, anterior pituitary and gastroenteropancreatic endocrine tissues [1]. Less frequent manifestations include adrenal cortex adenoma, foregut carcinoid tumor and subcutaneous lipoma. Some cutaneous tumors, such as collagenoma and facial angiofibroma, are also seen. A clinical diagnosis of MEN1 is made when at least two lesions in three principal organs (parathyroid, anterior pituitary and pancreas/duodenum) are confirmed [2].

Patients with MEN1 are at an increased risk of premature death. In earlier studies, the average life-span of patients was about 50 years [3, 4]. The predominant cause of death was peptic ulcer and subsequent complications caused by gastrinoma and hyperparathyroidism. Since medical management for peptic ulcers has been dramatically improved by the introduction of H2 blockers, the risk of such premature death has greatly decreased. In recent studies, the most significant determinant of prognosis in patients with MEN1 was the malignant transformation of gastroenteropancreatic tumors and thymic/bronchial carcinoid tumors [5–8]. Pancreas islet cell tumor occurs in about 50% of patients and often metastasizes to the liver and other organs. Thus, the early detection of such tumors is crucial to achieving a better clinical course and possibly to obtaining a better life expectancy. Periodic biochemical and imaging studies are therefore recommended [2].

The standard treatment for functioning pancreas islet cell tumors is surgery. Surgery is also the golden standard for the treatment of non-functioning pancreas islet cell tumor (NFPT), but its indications and timing are

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controversial [9–11]. In this study, we analyzed the long-term clinical courses and surgical outcomes, particularly the postoperative development of diabetes, of Japanese patients with MEN1-associated NFPTs.

Patients and Methods

Forty-three patients with MEN1 who were followed-up for more than two years between 1995 and 2004 in our hospital were analyzed. A diagnosis of MEN1 was made in probands with evidence of neoplastic lesions in at least two out of three principal organs (parathyroid, anterior pituitary and pancreas/duodenum). Among family members, a diagnosis was made with evidence of at least one lesion or confirmation of an *MEN1* germline mutation. The patient characteristics are summarized in Table 1. Patients were periodically examined using abdominal CT scanning (average interval, 17 months). An NFPT was diagnosed when the plasma or serum hormone levels (gastrin, insulin, glucagon and somatostatin) were within normal limits and no clinical symptoms attributable to hormonal excess were present.

Results

During the study period, 26 NFPTs were identified in 14 patients. The location, size and longitudinal course of each tumor are shown in Fig. 1 and Table 1. The average age at the time of NFPT diagnosis was 48 years (29–59 years), and the average tumor size was 20 mm (5–78 mm). Seven of the tumors were located in the pancreas head, 9 were located in the pancreas body, and 10 were located in the pancreas tail. Among the 26 tumors, 7 tumors in 5 patients (average size, 40 mm [15–78 mm]) were surgically removed within 3 months of diagnosis. In one case (Fig. 1 and Table 1, patient C), a 57-year-old man with a 50-mm tumor in the pancreas tail, multiple metastases to the liver were found at the time of the initial examination. After resection of the primary pancreatic tumor, he received a series of transcatheter arterial embolizations and combined therapy with interferon and a somatostatin analog for the treatment of the metastatic tumors. The patient died 2 years after undergoing surgery.

All the resected tumors were pathologically examined using hematoxylin-eosin staining and immunostaining for specific proteins, such as chromogranin A, NSE, insulin, and glucagons. All the tumors were positive for chromogranin A and NSE and some were positive for insulin, glucagons and pancreatic polypeptide.

Table 1. Patient characteristics

No. of patients followed between 1995–2004 (M/F)	43 (17/26)
with either a family history or an *MEN1* mutation (M/F)	36 (17/19)
age at diagnosis of MEN1 (yr, mean ± SD) (range)	41.7 ± 14.8 (14–74)
proband/family member	23/20
No. of patients with NFPT (M/F)	14 (7/7)
age at diagnosis of NFPT (yr, mean ± SD) (range)	48.4 ± 9.8 (29–59)
size of tumor (mm, mean ± SD) (range)	20 ± 18 (5–78)
follow-up period after NFPT diagnosis (mo, mean ± SD) (range)	78 ± 36 (27–115)

Indolent character of primary NFPTs

In general, we performed surgery to resect NFPTs that were larger than 20 mm in diameter. Two patients with large NFPTs (Fig. 1, patients E and F) refused surgery and preferred to receive periodical examinations. We followed 13 primary tumors for between 24 and 115 months. During the follow-up period, only one tumor showed a significant increase in size (>20%; 31 mm → 38 mm over the course of 109 months; Figs. 1 and 2, patient E); none of the other tumors exhibited significant growth.

Occurrence of newly developed NFPTs during follow-up

During the follow-up period, newly developed NFPTs were found in 6 patients (Fig. 1, patients A, B, D, E, H and K). All of these patients, except for patient H, had been diagnosed as having NFPTs at the beginning of the follow-up period. Among the 6 patients whose primary tumors were 35 mm or larger (Fig. 1, patients A to F), newly developed tumors or metastases were found in 5 patients. On the other hand, among the 8 patients whose primary tumors were 25 mm or smaller, newly developed tumors occurred in only patient K (Fig. 1).

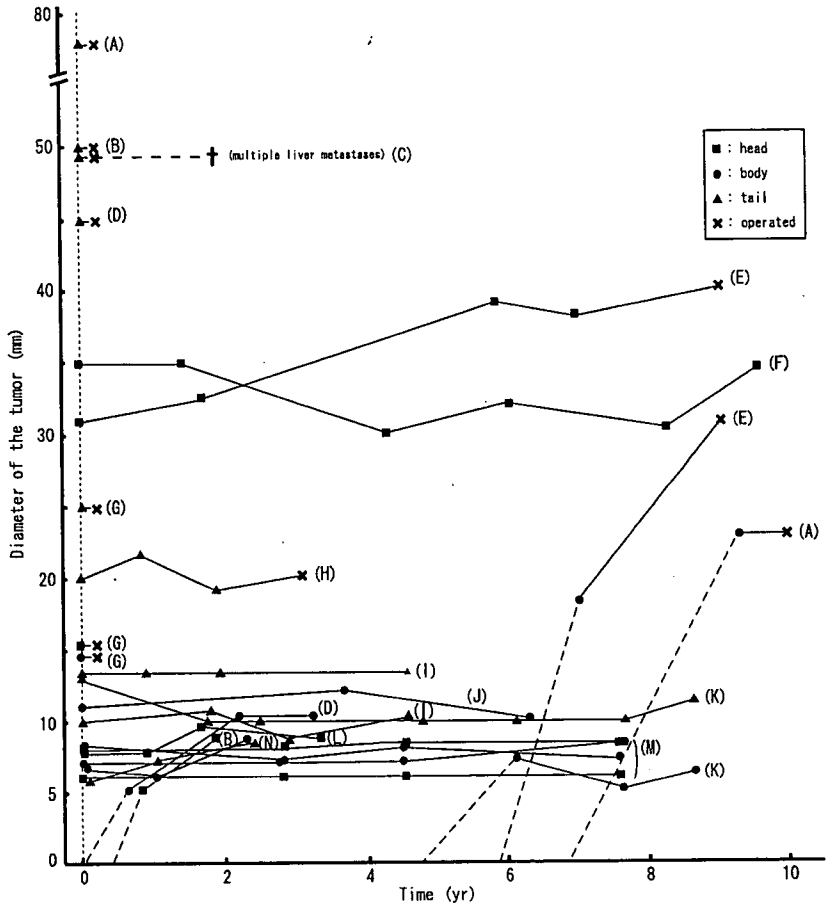

Fig. 1. Localization, size and longitudinal course of NFPTs in patients with MEN1. The ordinate axis indicates the diameter of each tumor, as estimated using computed tomography (CT). The abscissas axis indicates the time since the NFPT was identified using CT.

Rapid growth of newly developed tumors

Some of the newly developed tumors showed rapid growth. In patient E, who refused surgery for a large pancreas head tumor, a newly developed tumor (18 mm) that was found in the pancreas body grew to a size of 31 mm (Figs. 1, 2). In patient A, a tumor (23 mm) and lymph node metastasis were found 9 years after surgery for the primary tumor.

Development of diabetes after pancreatectomy (Table 2)

Among the 7 patients (patients A, B, C, E, G, H, and N) who had histories of partial pancreatectomies, only one patient remained euglycemic (patient G). Patient B, who had acromegaly and had undergone transsphenoidal surgery, had an elevated fasting glucose level (114 mg/dL). He is currently receiving octreotide injections to suppress tumor growth and hormone production from a remnant pituitary tumor. Recent laboratory results show a plasma IGF-1 level of 700–800 ng/mL. Thus, his glucose intolerance may have been caused by the uncontrolled acromegaly and octreotide injections, rather than the pancreatectomy. Patient C also received octreotide injections for the treatment of metastatic liver tumors. Among the 7 patients who did not receive a pancreatectomy or who received only tumor enucleation, only one patient (patient F) is currently diabetic.

Discussion

NFPT is the most common pancreas islet cell tumor

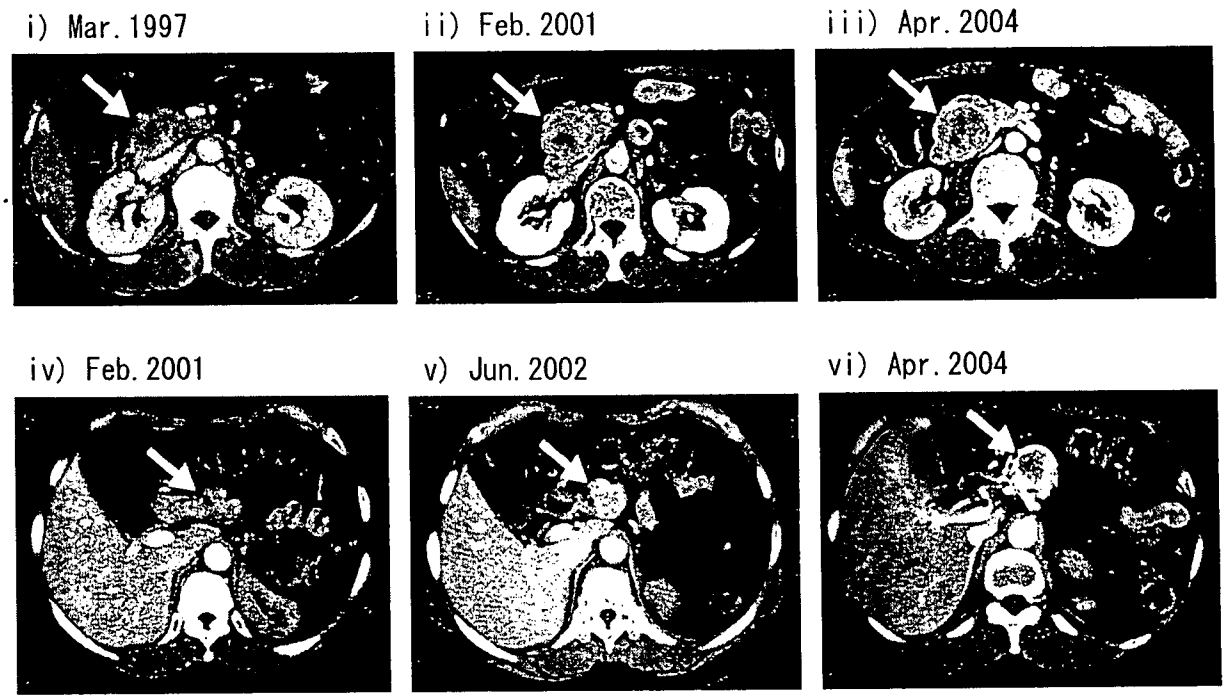

Fig. 2. Growth of primary and secondary NFPTs in patient E. Panels i) to iii) show the growth of the primary pancreas head tumor identified in 1997, and panels v) and vi) show the rapid growth of a secondary tumor in the pancreas body, which was not seen in panel iv).

Table 2. Clinical characteristics of patients with NFPTs

Patient	Age[1]	Sex	Tumor size (mm)[2,3]	Tumor localization[3]	Surgery	Glucose tolerance			
						before surgery[6]	after surgery[6]	HbA1c[8]	Medication[9]
A	57	F	78, 23	tail, body	distal pancreatectomy	NA	DM	7.0	SU + BG
B	29	M	50, (9)	tail, (head)	distal pancreatectomy	NGT	IGT	6.0	(LAR)
C	57	M	50	tail	subtotal pancreatectomy	NGT	DM	8.0	INS (OCT)
D	52	M	45, (10)	tail, (body)	enucleation	NGT	NGT	5.0	
E	51	F	38, 31	head, body	pancreaticoduodenectomy	NGT	DM	7.4	INS
F	49	F	35	head	—	DM		6.1	BG
G	43	F	25, 15, 15	tail, body, head	distal pancreatectomy + enucleation	NGT	NGT	4.2	
H	49	M	20	tail	distal pancreatectomy	DM	DM	7.0	INS
I	59	M	13, 10	tail, tail	—	NGT		5.4	
J	59	F	11	body	—	NGT		5.2	
K	36	F	13, 8	tail, body	—	NGT		5.2	
L	46	M	9	head	—	NGT		5.6	
M	34	F	8, 6, 7, 8	head (2), tail (2)	enucleation of insulinoma[4]	NGT		4.4	
N	57	M	9, 9	tail, body	pancreaticoduodenectomy[5]	NGT[7]	DM	6.6	none

[1] Age at diagnosis of NFPT.
[2] Diameter of the tumor at the last evaluation.
[3] Newly developed tumors after primary surgery are indicated in parentheses.
[4] Received surgery at age 13.
[5] Received surgery for a gastrinoma at age 54.
[6] DM, diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; NA, data not available.
[7] Before pancreaticoduodenectomy.
[8] Value at the last measurement. Normal range, 4.3–5.8%.
[9] INS, insulin; SU, sulfonylurea; BG, biguanide; LAR, long-acting octreotide; OCT, octreotide.

seen in patients with MEN1 [12, 13]. Reducing the risk of malignant transformation is the primary reason for surgical intervention for NFPT. Which treatment modality provides patients with the most favorable quality of life and life expectancy remains debatable. Some reports on preferable surgical treatment for sporadic NFPTs have been made [14–18], but whether these procedures are directly applicable to MEN1-associated NFPTs is uncertain. In sporadic NFPTs, surgical resection of the tumor can lead to a complete cure, but this is not the case for patients with MEN1, a life-long disease. Also, the clinical course of MEN1-associated NFPTs may not be the same as that of sporadic NFPTs [19].

A number of studies have reported a link between the size of MEN1-associated gastrinomas and the risk of distant metastasis [8, 20]. Accordingly, many experts have recommended that surgical treatment for gastrinomas should be performed only for large tumors [5, 21, 22]. For NFPT, the possibility of a correlation between tumor aggressiveness and size has been argued. Several studies have suggested that larger tumors are more aggressive, and have recommended that surgery should be considered only for NFPTs larger than 2–3 cm, while smaller tumors should be carefully surveyed [10, 23, 24]. Recently, Triponez *et al.* reported that surgery for NFPTs smaller than 2 cm is not beneficial for MEN1 patients, with regard to their life expectancy [25]. On the other hand, a poor correlation between tumor size and malignant behavior has also been documented [26]. Some groups advocate an aggressive surgical approach for MEN1-associated NFPTs [27–30]. The rationale for such aggressive management is based on the high malignant potency of NFPTs in MEN1. Indeed, malignant pancreatic tumor is the leading cause of mortality in patients with MEN1 [5–8], and NFPTs are widely recognized to have a higher malignant potential than functioning pancreas islet cell tumors. Nevertheless, the benefit of early surgical treatment of NFPTs in patients with MEN1 has not been fully established. Also, few studies have focused on the quality of life of patients who have undergone a pancreatectomy.

Our present results indicate that most NFPTs have an indolent clinical course. None of the small NFPTs (20 mm or less) showed growth during the follow-up period. Furthermore, the patients with small NFPTs did not develop metastasis to either the regional lymph nodes or the liver. This finding is in agreement with a recent report by Thomas-Marques *et al.* [12] showing that, in more than half of their patients, the diameter and number of NFPTs were stable during the follow-up period of their study. Since we experienced only two cases with liver metastases, we cannot provide any additional evidence as to whether tumor size and malignant potency are related. However, liver metastasis was only seen in patients with large NFPTs (78 mm and 50 mm). This finding was also true in a report by Lowney *et al.*, where the only patients with large tumors had liver metastasis [26].

On the other hand, some secondarily developed tumors in our cases showed relatively rapid growths. These tumors were seen in patients with histories of surgical resection for large primary tumors (patients A and E). Whether these rapidly growing tumors were metastasized from the primary tumor or *de novo* tumors is unclear, but the latter possibility is more likely since liver metastases were not seen in these patients. Also, in patient A, the secondary tumor appeared 9 years after the resection of the primary tumor (Fig. 1). These findings suggest that periodical follow-up after tumor resection is particularly important in patients with large NFPTs and that once a newly developed tumor is found, early surgical intervention or further close observation may be appropriate.

Aggressive surgical procedures certainly reduce the risk of metastatic disease and the development of other primary tumors arising from the residual pancreas. Some authors also claim that such procedures rarely result in the development of diabetes [31]. However, the impairment of glucose metabolism after a pancreatic resection is relatively common [32, 33]. Furthermore, an increased prevalence of diabetes in patients with MEN1 has recently been reported [34]. The effect of a pancreatectomy on glucose metabolism is particularly important in Asians, because this ethnic group is known to have lower beta cell function, compared to non-Hispanic whites and African-Americans [35, 36]. This fact raises the possibility that pancreatectomies may impair glucose metabolism more frequently in Asian patients. Although the available data was limited and was not adjusted for clinical parameters like age, sex, primary pancreatic disorders and preoperative glucose metabolism, Shibata *et al.* [37] reported that 3 of 7 Japanese patients who received a distal pancreatectomy developed substantial diabetes. In the present study, at least 5 of the 7 patients who received a partial pancreatectomy became diabetic. Three patients who

became diabetic after undergoing partial pancreatectomies were apparently euglycemic before surgery. On the other hand, among the 7 patients who did not receive a pancreatectomy or only underwent tumor enucleation, only one patient is currently diabetic.

Our study has several limitations. First, the number of patients was small and data was only obtained from a single institution, which may have causes an unintended bias with regard to the patients' backgrounds. However, we identified 14 out of 43 patients with MEN1, and this number is, to the best of our knowledge, one of the highest in Japanese patients' registries, since a nationwide registry system does not exist in Japan. A multicenter survey is certainly needed. Secondly, insulin secretion and insulin resistance was not estimated in each patient before and after pancreatectomy. Such evaluations will be essential to clarify the mechanism of the development of diabetes in the majority of patients who received a partial pancreatectomy. It should be noted that except for patient M, none of the patients were obese and their body mass indices were less than 25. Recently, Lee *et al.* reported that reduced insulin secretion, rather than insulin resistance, plays a major role in the development of diabetes in Korean patients who received distal pancreatectomies [38]. Reductions in insulin secretion almost certainly had a major contribution to the exacerbation of glucose metabolism in our patients who received pancreatectomies. To clarify the beneficial effect of a pancreatectomy for preventing the occurrence of malignant tumor and the risk of developing diabetes and subsequent complications, especially in Asian patients, the accumulation of more data and a prospective follow-up study is needed.

In conclusion, based on our current results, we agree with the proposal made by Triponez *et al.* [25] and recommend that NFPTs smaller than 20 mm should be observed, based on their indolent clinical course, low malignant potential, and the possible risk of postoperative diabetes. However, a subgroup of patients may suffer from more aggressive and often lethal complications of the disease. Our limited experience is insufficient to draw a definite conclusion regarding the surgical indications for MEN1-associated NFPTs. The accumulation of further data and a longer follow-up period is needed to strengthen our conclusions, and reliable markers for distinguishing less aggressive NFPTs from aggressive ones are needed.

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Case Report

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Community Engagement and Informed Consent in the International HapMap Project

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Key Words
Community engagement · Community consultation · Public consultation · Informed consent · International HapMap Project · Genetic variation research

Abstract
The International HapMap Consortium has developed the HapMap, a resource that describes the common patterns of human genetic variation (haplotypes). Processes of community/public consultation and individual informed consent were implemented in each locality where samples were collected to understand and attempt to address both individual and group concerns. Perceptions about the research varied, but we detected no critical opposition to the research. Incorporating community input and responding to concerns raised was challenging. However, the experience suggests that approaching genetic variation research in a spirit of openness can help investigators better appreciate the views of the communities whose samples they seek to study and help communities become more engaged in the science.
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Background

The International HapMap Consortium has completed the first phase of the International HapMap Project, an effort to develop a haplotype map of the human genome that describes the common patterns of DNA sequence variation [1]. The HapMap will be used as a resource to facilitate future studies that relate genetic variation to health, disease and drug response [2].

DNA samples from 4 populations were studied in the first phase: Yoruba from Ibadan, Nigeria; Japanese from Tokyo, Japan; Han Chinese from Beijing, China; CEPH (Utah, US residents with northern and western European ancestry; table 1). Investigators in Japan, the UK, Canada, China and the US analyzed all samples across the genome to determine their haplotype structure (the patterns of genetic variation). Based on the data generated, future investigators searching for genes that contribute to disease will be able to choose tag single nucleotide polymorphisms (SNPs, or sites in the DNA sequence where individuals vary) that they can use to conduct their studies much more efficiently.

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Table 1. Populations included in developing the genome-wide HapMap

Population	Samples collected	Criteria for defining population membership
Yoruba in Ibadan, Nigeria (YRI)	parent-adult child trios	4 of 4 Yoruba grandparents
Japanese in Tokyo, Japan (JPT)	unrelated individuals	'aim to collect from individuals whose grandparents were all Japanese'
Han Chinese in Beijing, China (CHB)	unrelated individuals	at least 3 of 4 Han Chinese grandparents
CEPH (CEU) (Utah residents only; individuals with Northern and Western European ancestry)	parent-adult child trios	not stated*

* The original aim was to collect samples from large three-generation families suitable for the construction of genetic linkage maps.

In a later phase, samples from several additional populations will be analyzed across a subset of genomic regions to assess how well the tag SNPs based on the data from the 4 initial populations will work in other groups. If these tag SNPs do not adequately capture the haplotype patterns in those populations' samples, additional tag SNPs based on the data from these populations may need to be identified and added to the database. Eventually, other investigators will likely provide data from other populations.

The blood samples collected to develop the HapMap were transformed into cell lines at the National Institute of General Medical Sciences (NIGMS) Human Genetic Cell Repository at the not-for-profit Coriell Institute for Medical Research in Camden, New Jersey. The Coriell Institute makes the cell lines and DNA available both to Project investigators and to investigators conducting other genetic variation research approved by the institutional review board (IRB). The samples have no individual identifiers or associated medical information. However, each sample set is identified with a population label, so that investigators can compare patterns of genetic variation not only among individuals, but among groups. This facilitates the selection of optimal tag SNPs for use in genetic association studies in specific study populations. However, labeling the populations raises complex ethical and social issues, because all members of a population and of closely related populations may be affected by the research, regardless of whether they personally donated samples.

For this reason, and because of the wide range of cross-cultural issues raised in a large, complex international study of this type, the Project devoted considerable time and resources to addressing the ethical and social issues. Bioethicists as well as social and behavioral scientists worked alongside genomics researchers in formulating important aspects of the study design. The Project also implemented processes to engage a range of people in each of the communities approached for the donation of new samples as well as a rigorous informed consent process, so that both individual and group concerns could be anticipated, understood and, to the extent possible, addressed. In this paper, we describe these processes, review some preliminary impressionistic findings and explain how the Project responded to some issues raised. An earlier paper provided a general discussion of the ethical, social and cultural issues the Project raises [3]. Later articles will describe in detail the methods and findings from the individual sites discussed in this paper and from the additional communities approached for later participation.

Populations and Communities

While recognizing the considerable complexities inherent in defining such terms as 'population' and 'community', for the purposes of the Project, a 'population' was defined as a group of individuals who have a common geographic ancestry, while a 'community' was defined as a group within a population with many local units of social organization [4]. The scientific, ethical and practical rationales for the decisions about which populations to include and which specific communities to engage, in the initial iteration of the HapMap, have been previously described [1, 2].

The CEPH samples studied for the Project were collected in 1980 from residents of Utah whose recent ancestors came primarily from northern and western Europe. The label CEPH is an acronym for the Centre d'Etude Polymorphisme Humain, the organization that originally collected the samples. Cell lines for the CEPH samples have been publicly available since 1992 from the Coriell Institute, and the samples have been used in numerous previous genetic studies, including the development of the human linkage map. HapMap investigators wanted to build on this valuable body of existing data, and thus chose to use a subset of these same samples to develop the HapMap. Although the original complete CEPH sample set includes some samples from individuals in France and Venezuela and individuals identified as Amish from Pennsylvania, only samples from the Utah CEPH donors were used for the Project. Although the CEPH population is the only one whose samples are included in the HapMap to be known by an acronym, investigators chose to retain this population label for the Project so that the HapMap data could be readily integrated with preexisting data from other studies of these samples without engendering confusion within the scientific community.

The consent process originally used to collect the CEPH samples, while quite comprehensive, did not meet the stringent standards established for the Project. However, because the investigators who had collected the CEPH samples had retained links to the donors' identities and had developed trust relationships with many donors, it was feasible for them to recontact most of the still living donors to seek new consent for their samples to be used specifically to develop the HapMap. The local IRB gave permission for deceased donors' samples to be used. Because the local IRB required the maintenance of absolute confidentiality with respect to the identities of the CEPH donors (who are known to others in their own families, but not to any other CEPH donors), it was not feasible to reconvene the CEPH donors as a group for a formal community engagement process analogous to that conducted for the Yoruba, Japanese and Han Chinese.

Unlike the case with the other 3 populations whose samples were studied, the criteria used to assess ancestry to determine eligibility for sample donation were not specified in the case of the CEPH donors. This again, however, reflects merely the historical reality that it was not the norm to explicitly define the criteria for population membership when the CEPH samples were collected. What is known is that all the donors resided in Utah and that most of their recent ancestors (like the recent ancestors of most Utah residents in the areas where the samples were collected) came from northern or western Europe [5].

The Yoruba samples were collected in Ibadan, the second largest city in Nigeria, with a population of nearly 2 million. The Yoruba are predominantly urban dwellers with a complex population history and a complex political and social organization. The group constitutes the majority population in Ibadan and approximately 30% of Nigeria's total population. Around 40 million individuals throughout West Africa self-identify as Yoruba [6]. Through previous research collaborations, the investigators enlisted to collect the samples had already developed a close working relationship with a Yoruba community in a particular area of metropolitan Ibadan. A robust approach to community engagement was thus designed to include as many community members as possible. To be eligible for sample donation, individuals were required to have 4 of 4 grandparents who self-identified as Yoruba.

In Japan, because of the population's relative ancestral homogeneity, it would have been possible to approach people for participation almost anywhere in the country. However, the sample collection took place in Tokyo, which draws people from all geographic areas of Japan. It included individuals who were, for the most part, already accustomed to participating in research. Individuals wishing to donate were simply told that the aim was to include samples from persons whose grandparents were all from Japan; donors were not asked whether they had a certain number of grandparents 'born in Japan' because it was thought that some people might find this question culturally insensitive. People from many parts of Japan, and especially from the Kanto area surrounding Tokyo, participated in the community engagement activities. Thus, people from a wide range of backgrounds were consulted. In addition, some input was obtained through conference presentations in several other countries.

The Han Chinese population is the largest of 56 ethnic groups in China; about 90% of all Chinese people self-identify as Han [7]. The specific community involved encompassed the entire residential community at Beijing Normal University (BNU), which includes almost 35,000 people, nearly all of Han ethnicity. Due to the wide geographic area and range of backgrounds from which BNU draws its residents, the community engagement, while situated in an academic environment, drew individuals with a range of backgrounds and ages. These individuals came originally from 22 of 34 Chinese provinces, autonomous regions, municipalities and special regions. For reasons of practicality, individuals who were approached to donate

samples were told that they should have at least 3 out of 4 grandparents born in China who self-identified as Han. However, given the BNU community demographics, all 4 grandparents of most donors were presumably Han.

Goals and General Approach

The goals of the individual informed consent process were to provide prospective sample donors with the information needed to ensure that their decision to donate was voluntary and informed. The goal of the community engagement processes was to give a broad range of members of the communities approached for participation an opportunity:

- to share their views about the ethical, social and cultural issues the Project raised for them, their immediate communities, and the broader communities and populations of which they are a part
- to provide input into such matters as how the samples from their locality would be collected and described
- to obtain extensive information about the Project so that the decisions of individuals whether to donate would be better informed
- to remain informed about how the HapMap and the samples are being used and about findings from future studies based on the HapMap or the samples.

Because it would have been impossible to seek input from all, or even most, people around the world who shared the relevant population labels, we focused our efforts primarily on the level of the specific localities from which we hoped to recruit donors. We recognized the significant limitations inherent in this approach, but reasoned that through in-depth, detailed inquiries in these communities, using a range of methodologies, we could reach a reasonably large and diverse range of individuals who, by virtue of sharing the same population labels with the actual sample donors, would most likely be affected by the research.

The aim of the engagement processes was not to achieve consensus or 'community consent,' even within these selected localities, nor to seek lay input into the advisability, as a matter of science policy, of launching a project of this type. In this respect, the approach differed from the 'participatory action' research model used in some studies of public health interventions, in which communities advise investigators on research priorities and have considerable input into major aspects of study design. The approach also differed from the formal community consultation processes required when conducting research in communities with sovereign status or highly organized political structures, such as American Indian tribal communities.

The specific approaches employed at each site to engage communities and to elicit individual informed consent were informed by relevant sets of then-existing local, national and international guidelines [8–17]. The activities were conducted under the auspices of local ethics committees.

Investigators were also guided by the community consultation policy of the NIGMS Human Genetic Cell Repository at the Coriell Institute (http://ccr.coriell.org/nigms/comm/submit/collpolicy.html). This policy requires some form of community consultation or engagement, tailored to local cultural norms, before the repository will accept any new samples with population identifiers for its genetic variation panels. It also provides for the establishment of a community advisory group (CAG) in each community where new samples are collected, to serve as a liaison between the community and the Coriell Institute to ensure that all research using the samples is consistent with the terms of informed consent (see Appendix 1).

In China and Japan, the community engagement/public consultation and sample collection activities were funded by those countries' participating genotyping centers, and local investigators conducted the work. In Nigeria, the work was funded by the US National Institutes of Health (NIH) and conducted by US investigators in collaboration with local investigators. The NIH also funded the process of obtaining new consent from the CEPH donors and the collection of samples from the additional populations whose samples will be studied in a later phase. At each site where new samples were collected, the community engagement and sample collection teams included individuals trained in genetics, individuals with background or training in bioethics or social science, and others (table 2).

Methodologies for Engaging the Communities and Obtaining Informed Consent

At all 3 sites where participants were approached to donate new samples, protocols were developed to engage the communities; these protocols were separate from those used to obtain individual informed consent. As noted earlier, community engagement of the CEPH donors, at least in a form analogous to that used with members of the other 3 populations, was not feasible because of IRB-imposed constraints related to individual donor

Table 2. Community engagement/public consultation teams

Population	Investigators	Institutions	Backgrounds
Yoruba	Charles Rotimi	Howard University	genetic epidemiology
	Clement Adebamowo	University of Ibadan	epidemiology
	Patricia Marshall	Case Western Reserve University	anthropology/bioethics
	Charmaine D.M. Royal	Howard University	genetics/bioethics
	Ike Ajayi	University of Ibadan	epidemiology
	Toyin Aniagwu	University of Ibadan	nursing
	Chibuzor Nkwodimmah	University of Ibadan	nursing
Japanese	Ichiro Matsuda	Health Science University of Hokkaido	genetics medicine
	Darryl Macer	Eubios Ethics Institute	bioethics
	Eiko Suda	Eubios Ethics Institute	bioethics
	Yoshimitsu Fukushima	Shinshu University	genetics
Han Chinese	Houcan Zhang	Beijing Normal University	psychology
	Changqing Zeng	Beijing Genomics Institute	molecular biology
	Hui Zhao	Beijing Genomics Institute	genetics
CEPH	Mark Leppert	University of Utah	genetics
	Missy Dixon	University of Utah	psychology
	Andy Peiffer	University of Utah	medicine

privacy. At the other 3 sites, however, no individual was approached to donate a sample until the process of community engagement was already well underway. Copies of the consent forms were distributed widely in each community from the Project's inception, however, to introduce the study and initiate discussion about its potential risks and benefits.

Templates for an informed consent form for sample donation and to obtain new consent from the living CEPH donors were developed by an initial planning group, with input from bioethicists, social and behavioral scientists, and geneticists. Each team of investigators responsible for community engagement (or, in the case of the CEPH donors, the team responsible for obtaining new consent) modified the consent documents as needed to make them culturally appropriate for their locality. Individuals in the communities where new samples were collected were subsequently given an opportunity to provide direct input into the consent form, although that process in most cases did not lead to substantive modifications. Both the modified informed consent forms and the sample collection protocols were reviewed by IRBs or ethics committees at all the institutions involved.

The specific approaches to engaging the communities and obtaining individual informed consent varied among the sites because of the vastly different community structures and cultural norms. In the Yoruba community approached for participation, it was necessary formally to consult a community leader (the Baale) before any individuals were approached. In China, investigators secured cooperation from the BNU administration and several academic departments before beginning their work. In Japan, where most of the work was carried out in a large urban area and the community was more loosely organized, the approach was more open ended.

For the CEPH, where the samples had already been collected and where thus, for historical reasons, the donors could not technically be engaged as a 'community' but instead only as individuals or families, the donors were merely approached to give new consent, using an individualized or family-based approach instead of a group-based process. Because of the continued interactions with the donor families, investigators were able to locate 44 of the original 47 families. Many were already involved in a separate ongoing genetics research project that required them to return periodically for follow-up. This gave investigators an opportunity to discuss the HapMap Project in person with them. Those donors who had already revisited the investigators were contacted by mail, with telephone follow-up. The remaining donors who had not been in recent contact or who did not initially reply were visited at home or called by a study co-