**Table 3.** Methodologies

| Population | Individual interviews | Focus groups | Public meetings | Attitudinal surveys | Other |
|---|---|---|---|---|---|
| Yoruba | 7 | 1 | 3 | 231 | initial working group |
| Japanese | 20 | 8 | 5 | 377 | 5 conference presentations; 10 explanatory meetings |
| Han Chinese | 100 | 6 | 3 | 130 | production of 9 min video compact disc (VCD) used to introduce the project to interviewees |
| CEPH (new consent) | | | | | personal visits, mail contact, telephone follow-up |

ordinator, who explained the Project in detail and gave them a chance to discuss it and ask questions.

Language and comprehension issues presented a major challenge during the community engagement and informed consent processes (see Appendix 2). Thus, open-ended discussions about the Project and the issues that it raises were encouraged. Major points contained in the consent form were explained orally and individuals seeking additional clarification had an opportunity to ask questions. In Nigeria, depending on their preference, participants were administered the informed consent procedures orally or in writing, either in English or Yoruba.

A detailed description of the methodologies employed for the community engagement activities at the 3 sites where new samples were collected is beyond the scope of this paper, but will be outlined in separate papers by the investigators from each site. Methodologies ranged from the use of extended, semistructured individual interviews and focus groups to large public meetings or lectures (followed by discussion) and public attitudinal surveys (table 3). The extensiveness of the processes employed varied considerably among the sites due to differences in the level of funding available for these activities. The empirical rigor of the processes for collecting and analyzing the data also varied somewhat from site to site. However, the processes were not specifically designed to provide data that were explicitly comparable across sites. The processes were rather designed simply to elicit the views of a range of people within each community, including those skeptical about genetics research, to glean general impressions (which in some instances could be little more than anecdotal) about the acceptability of the goals of the Project and other pertinent issues. Open discussion was encouraged at each site so that investigators could be alerted to any specific concerns and address them to the extent possible. Thus, participants at each site were asked about their attitudes toward genetic research in general and genetic variation research in particular (including research like the HapMap, which would have no immediate health benefits). Participants were given an opportunity to raise concerns about proposed methods of recruitment, privacy and confidentiality risks, risks of discrimination or group stigmatization, issues relating to commercialization and intellectual property, and any other pertinent matters.

### Specific Elements of the Informed Consent Process

The consent process explained how the HapMap would be developed and used in future studies to find genes that affect diseases, drug response and other traits. Prospective donors were told that neither names nor medical information would be taken – only the name of the population from which the donor came – and that more samples would be collected than would be used, as an additional protection of individual privacy. For the CEPH donors, links to the donors' identities exist, but only the investigators who collected the samples – not the repository, HapMap investigators or any other investigators who order the samples – have access to this information.

Prospective donors were also told during the consent process that the samples would be sent to the Coriell Institute, transformed into cell lines and made available to Project investigators and other investigators worldwide for use in future genetic variation studies. All such future studies, however, need to be approved by the repository's IRB (and any other relevant ethics committees) to ensure that the proposed research is consistent with the terms of the consent form.

Because no individual identifiers are available for any of the newly-collected samples, it will not be possible to recontact donors in the future to seek their consent to other studies. However, the consent form described the general nature of future studies for which the samples and the HapMap may be used, such as studies of the biology of DNA, how new variations arise, the genetic history of human groups, and how people from different parts of the world are related. The consent form also expressly authorized use of the samples for gene expression studies, but forbade their use for reproductive cloning. The reference to cloning was included because of concerns expressed in some communities about this possibility. It was explained that the risks raised by the types of future studies authorized in the consent form are unlikely to be different in kind from the risks raised by the Project itself.

Prospective donors were also told that because of the absence of individual identifiers, donors could neither receive individual feedback on the research findings nor individually withdraw their samples or data. However, in each community where new samples were collected, it was explained that a CAG would be established, through which the community would be able to stay informed about general findings and how the HapMap and samples are being used. Prospective donors were also informed that a community could request, through its CAG, that all of its samples be withdrawn from distribution in the unlikely event that a serious disagreement about future uses of the samples arises that cannot otherwise be resolved.

Prospective donors were informed that the HapMap would be publicly available in a database on the Internet. It was explained that the genetic information available about each donor would be quite extensive, but that it was very unlikely that any information could be linked to a specific donor, at least without having another sample from the donor for comparison.

Prospective donors were also told that they would receive no immediate health benefits from donating samples; any benefits would likely come only in the future, as investigators use the resource to find genes related to disease and then gradually develop improved methods of prevention, diagnosis and treatment. Donors were also informed that they would receive no financial benefits from participation, except for nominal compensation for their time and travel. They were further advised that while the Project itself would generate no commercial products, such products might be developed from other studies based on the stored samples or information in the HapMap, and donors would not be able to share in any such profits.

The consent form specifically mentioned the potential group risks associated with genetic variation research, such as risks of group stigmatization or discrimination (if investigators in future studies were to find that genetic variants associated with a particular disease were more frequent in people from their group and this information were overgeneralized to all or most members of the group or to related groups). It was also explained that focus on group differences might 'reify' notions of race, thus potentially exacerbating societal prejudices.

In the Yoruba community, where investigators collected samples from parent-adult child trios, the procedures for handling findings of misattributed paternity or undisclosed adoption were also described; these procedures had been similarly described to the members of the CEPH donor families at the time the CEPH samples were originally collected. Prospective donors who were concerned that someone in the family might not be biologically related were advised that they could, but did not have to, disclose this information. The Coriell Institute would test all samples in the trios for relatedness and if it were to be found that not all family members in a trio were biologically related, no one would be told and the samples simply would not be used for the HapMap.

Although the Coriell Institute routinely tests all samples it obtains for the presence of HIV (and destroys any found to be infected), the Yoruba sample collection team decided to require HIV testing of all prospective donors prior to donation (with the opportunity for follow-up referrals and treatment where indicated). All the relevant IRBs approved this procedure. Yoruba community members viewed the opportunity for free HIV testing as a form of benefit associated with Project participation (although no one who underwent the testing had a positive test result). A separate process was used to obtain informed consent for the HIV testing.

### Perceptions of Risks and Benefits

It is impossible to generalize from the perceptions of potential risks and benefits expressed by a small subset of individuals in the few specific localities where we did our work to everyone in these communities or to other communities. As noted earlier, most community engagement activities were designed to glean only general impressions about reactions to and concerns about the Project, and not as rigorous empirical data gathering exercises. The

general responses from those who took part in the community engagement activities are, however, instructive in demonstrating a range of perceptions about genetic variation research.

While the scientific details of the Project seemed difficult for many people to understand, most individuals – even in instances where substantial linguistic and educational barriers were present – appeared to comprehend the Project's general purpose, as judged (albeit imperfectly) by what they communicated to investigators when asked to explain their understanding of why they were being asked to give samples. They also appeared to be able to understand that they would receive no immediate personal health benefits by participating but that future generations might benefit.

People consulted in Japan expressed a diversity of views, ranging from skepticism, through indifference, to a generally positive attitude about the potential of genetic variation research. A similar range of views was expressed in the BNU Han Chinese residential community, but among most people there, the Project was quite favorably received.

The Yoruba community as a whole demonstrated considerable enthusiasm about the Project. Many individuals expressed a strong sense of pride that their community had been selected as a possible sampling site for a major international biomedical research effort, especially when the 'Out of Africa' theory of human population history was discussed. Several people there commented that genetic variation research, by demonstrating people's biological relatedness, might in some way help bring the world's people together – especially Yoruba or other people with African ancestry separated from their roots through slavery. Few people, even when probed, expressed concern that the Project could exacerbate racial or ethnic divisions.

Among the CEPH donors approached for new consent, stated reactions to the Project were generally quite positive, as reflected in the fact that to date, 367 living individuals including third-generation offspring (far more than the number whose samples were needed) have consented to their samples being used, either for the HapMap or for other genetic variation research. Where investigators had the opportunity to discuss the Project in person, 95 out of 95 individuals agreed to participate. This very high rate of acceptance of the Project among the CEPH donors may, of course, be primarily a reflection of the relatively high socioeconomic status of this particular group of donors, coupled with their long, successful history of collaboration in other genetic studies; it is unclear how generalizable this finding would be to other groups.

Some specific concerns about the Project were expressed. Although the data from each site have not yet been fully analyzed, a preliminary review suggests the emergence of a few predominant themes in each community.

Among the Yoruba, where most of the participants in the community engagement process were lay individuals with no background or training in biomedical research or related issues, the most frequent concerns raised were about:

- the physical process of blood drawing
- how the blood samples would be handled
- the disposal plans for the blood samples that were not used.

In Japan, where many though by no means all of the individuals approached had some sophistication about biomedical research, the main concerns expressed were about:

- privacy and confidentiality
- how the samples would be labeled
- whether the HapMap would somehow be used to try to define genetically who is a 'real' Japanese person
- the potential for discrimination against minority groups in Japan and against Japanese people living as minorities in other countries
- the potential for commercial use of the stored samples, especially by US biotechnology companies
- how adequate oversight over the samples would be ensured once the samples had been sent to a US repository.

In China, where the community engagement process involved a broad range of individuals, with varying degrees of sophistication regarding biomedical research, the main concerns (although voiced by only a few participants) were that:

- the Project would not include samples from all ethnic groups in China
- the samples might be used for reproductive cloning
- information from the samples might be used for forensic purposes
- the blood drawing might cause infection
- personal genetic information might be 'leaked' outside the Project
- knowledge derived from the Project could lead to discrimination (although few people reported that they thought the Project itself would exacerbate racial or ethnic tensions).

A few CEPH donors asked to give new consent to have their samples used for the Project questioned whether by allowing this, their privacy and the strict controls on access to phenotypic information would continue to be maintained rigorously. These donors were reassured, however, when it was explained that the HapMap would include no individual identifiers and that the links to the identities kept by the local investigators would never be shared with other Project investigators, the repository or any future investigators who may use the samples (except for collaborators of the sample collectors).

### General Reactions to Genetic Variation Research

Despite the occasional expression of the concerns outlined above, we detected no critical opposition to the Project or to genetic variation research in general, at any of the sites. In particular, we found what appeared to be an absence of widespread concern about the potential for group stigmatization that might result from studies that use the HapMap. While some critics of genetic variation research might interpret this as indicative of people's naiveté or inability to understand the Project, some alternative explanations are plausible.

One explanation is that most of the people approached for participation were living in societies that were either racially or ethnically quite homogeneous (in the case of the Japanese) or in nonhomogeneous societies where they were members of the majority populations (in the case of the Yoruba and Han Chinese), and this circumstance may have considerably influenced their viewpoints. For example, in Nigeria, because most individuals' ancestors come from the African continent, considerably less 'race consciousness' can be observed than exists in the US, for example. Many Nigerians do have a strong sense of ethnic identification, but few people expressed concern that genetic variation research alone was likely to have much impact on ethnic divisions within the country or more broadly. Japan is a relatively ethnically homogeneous society, and in China the specific community engaged was composed almost exclusively of individuals from the majority (Han) population. Also, in both Japan and China, as in Nigeria, racial issues do not figure nearly as prominently in most people's thinking as they do in the thinking of people from Western countries.

Individuals' and communities' conceptions of the risks associated with genetic variation research can be expected to vary, depending on how they construct their social identities and how those identities are perceived by others. For this reason, we must acknowledge that we may well have encountered many more expressions of skepticism about the Project had we actively sought out the views of minority group members (for example, Korean or Chinese individuals living in Japan, members of some of the non-Han ethnic groups in China, or members of some of the numerous ethnic groups in Nigeria that are smaller and thus potentially more vulnerable than the Yoruba). Indeed, members of some such groups might have wondered why samples from their populations were being 'excluded' from study – a circumstance that underscores the need for sustained engagement activities with more broadly based participation. We also do not know how similar groups in other countries, or groups perceived by others as similar to those participating in the Project, conceive risks associated with this research. This must be regarded as a significant limitation of these preliminary findings from the community engagement activities.

It is unclear whether the generally positive views about this type of research expressed by those with whom the Project has been discussed so far will turn out to be shared by most of the rest of the public, as awareness of the Project around the world grows. It is, however, worth observing that historically, concerns about the potential of genetic variation research to exacerbate forms of racism or ethnic tension, and about the tendency of such research to overfocus on genetics instead of the environment as a major causative factor in disease, have often emerged not so much from grassroots lay communities as from segments of the bioethics, social scientific and other professional communities. This is not to suggest that these concerns are without any basis, but merely to note that they may not be as widely shared by members of the public as some might assume. It will be instructive to learn how members of the additional populations approached for participation in a later phase of the Project – some of which are racial and ethnic minorities in the US – will react to the research.

### Incorporating Community Input

While many scientific aspects of the Project design were essentially fixed for scientific reasons, limiting the extent to which communities could alter the study design, certain practical aspects of the recruitment and sample collection processes were modified in direct response to information obtained in community discussions. One especially important matter on which com-

munity input was weighed was how to label each population's samples and associated data. An exception to this were the CEPH donors, where, as discussed earlier, a formal process of community engagement was not feasible, where the acronym 'CEPH' had already been chosen when the samples were first collected, and where adopting a different label for these samples for this Project would likely only have engendered confusion in the scientific community.

In the places where new samples were collected, however, deciding how to label the samples required the disentanglement of complex notions of socially and genetically defined identity. While the selection of populations to be included in the Project was based on ancestral geography, the communities engaged in or consulted for the Project were, for the most part, composed of people with a range of *socially and culturally* (not genetically) defined identities. For example, some individuals in the Ibadan, Nigeria community engaged for participation considered themselves socially or culturally Yoruba even though they were not technically eligible to donate because not all of their grandparents were members of that specific ethnic group. Some individuals in the BNU residential community, while identifying as Han Chinese, may have had recent ancestors of other Chinese ethnicities. A small number of people in Japan who identify as, and culturally are, Japanese have some recent ancestry from Korea or other parts of Asia. In many of these cases, moreover, the basis for these individuals' constructions of their social identities is unknown by others. Many individuals also construct their social identities primarily around religious, political or other affiliations, not around ethnicity or ancestry. In addition, some individuals – perhaps most – view themselves simultaneously as belonging to several groups.

Thus, while each community provided input into how its population's samples should be labeled, the final decisions about labeling were based on a mix of community input and scientific, ethical and practical considerations. For example, in Japan, where this issue was discussed extensively, the names 'Asian' and 'East Asian' were rejected because these broad geographic areas include much greater ancestral diversity than just Japanese. Ultimately, the more specific descriptor 'Japanese in Tokyo, Japan' (JPT) was chosen. Likewise, because Han is only one of many Chinese ethnicities, the label 'Han Chinese in Beijing, China' (CHB) was chosen over the more general descriptor 'Chinese', and 'Yoruba in Ibadan, Nigeria' (YRI) was chosen over such terms as 'African', 'Sub-Saharan African', 'West African' or 'Nigerian'. To avoid overgeneralizing the results from any studies of these samples, users of the HapMap and of the samples are directed to a page on the Project website that explains the importance of using these specific terms, and not, for example, using 'African' for the Yoruba samples (http://www.hapmap.org/citinghapmap.html.en).

Our experience suggests that discussing the pros and cons of particular population identifiers with communities can be instructive – both to help communities understand the rationale for the study of genetic variation and to help investigators understand how people's own socially constructed notions of identity may differ from the identities geneticists seek to ascribe to them. This ultimately contributes greater rigor to the way the data are interpreted. Such discussions can also help elucidate other community concerns. For example, investigators may learn that a particular locality does not want its specific name used to better preserve its privacy.

### Responding to Community Concerns

During the course of engaging the communities, several issues arose that necessitated a considered response. For example, Yoruba community leaders used the occasion of a site visit by a staff member from the NIH (the agency that funded the community engagement) to request funds to contribute to the building of a local health center. Emerging local standards of bioethics in Nigeria, as stated in that country's proposed National Code of Health Research Ethics, direct that in certain international collaborative studies, 'research should be integrated with comprehensive capacity building, technology transfer and health care delivery strategies that address significant local health problems' [18]. Consistent with this guideline, and in recognition of the fact that Nigeria, unlike the other participating countries, would receive no benefits from participating in the genotyping (the most heavily funded part of the Project), the NIH had already provided modest funds at the beginning of the Project. These funds had been used to enhance the basic preventive and primary care services already available locally and the local collaborators received training and equipment. However, later in the course of interacting with the community, some additional funds were sought as a demonstration of reciprocity for the community's contribution to the Project.

When the request was made, the community had already committed itself to participating and sample collection had already begun. Thus, there was little potential

for undue influence; individual participants there, as in all communities, were compensated only for time and travel. Nonetheless, deciding how to respond to the request raised ethical and practical challenges.

Several factors argued in favor of providing such funds. First, as already noted, unlike in the 3 other countries, where local investigators benefited directly by participating in the genotyping, no one in Nigeria was in a position to do this, and thus that country was differently situated. Coupled with this, the HapMap itself also will provide no direct, immediate health benefits to donors; yet the samples will be made available to multiple investigators around the world, including many in biotechnology and pharmaceutical companies in countries with better-developed biomedical research infrastructures. These investigators will receive considerable financial benefit from future studies based on the HapMap, as they develop and commercialize useful therapeutic and diagnostic applications. Realistically, these applications will take much longer to reach Nigeria than countries with better-developed health care delivery systems.

On the other hand, some members of the Project's Ethical, Legal and Social Implications Group and of the Project's Steering Committee were concerned that providing the requested funds might create a troublesome precedent, leading to a climate in which future investigators – especially local investigators without support from large funding agencies – would find it hard to conduct their studies. Questions were also raised about potential inequities with other participating HapMap communities. Existing sets of international guidelines on biomedical and research ethics provided limited help. While such guidelines recognize the appropriateness of providing capacity building or other forms of community benefit, especially for population-based studies carried out in resource-poor countries [8, 9, 11, 19, 20], and while Nigeria's own proposed National Code of Health Research Ethics specifically recognizes the appropriateness of such strategies [18], the rules of most funding agencies, including the NIH, do not explicitly recognize 'capacity building' as an allowable cost item.

In the end, the NIH did offer – with approval from the relevant ethics committees and IRBs in Nigeria and the US – the provision of some additional funds to compensate for various tangible cost items that had not earlier been provided for, subject to the receipt of the documentation to support their disbursement. These funds will be released to the chair of the CAG and another named community leader, who will hold them in trust for the community. The community may then choose to use the funds to contribute toward the desired health center, along with funds being sought from other sources.

The Project was similarly challenged to respond to some issues that arose in the course of the community engagements in China and Japan. In both countries, concerns were expressed about whether the Coriell Institute would provide the communities (through the CAGs) sufficient information on an ongoing basis to enable them to assess whether the samples really were being used in the agreed-upon ways.

In response to these concerns, the Coriell Institute modified its Statement of Research Intent, a form that all investigators who order samples must submit. Investigators who order the samples are now required to include a statement describing their proposed research in terms that lay people can understand. These statements are then provided to the CAGs by the Coriell Institute on a quarterly basis, along with a list of the names and institutions of the investigators who requested the samples. As negotiated with the communities, each quarterly report also includes a listing of all HapMap Project publications, major publications from studies that have used the HapMap and major publications from other studies that have used the community's samples. Periodic newsletters, translated into the languages of all participating communities, are also produced; these include additional information about the Project, the participating communities and how the HapMap is being used. The newsletters are made available both to the CAGs (for further dissemination within each community) and to the public through the Coriell Institute website (http://coriell.umdnj.edu/ccr/hapmap.html). CAG members are invited to suggest to the Project management and the repository ways to improve the usefulness of the information disseminated.

In further response to concerns initially expressed in China and Japan about sending their samples to a US repository, the Director of the Cell Repositories at the Coriell Institute traveled to meet with CAG members in both countries. A similar visit to Nigeria is being discussed. These visits, which also included Project representatives from the NIH, provided an opportunity for community members to learn about the repository's commitment to serve as a responsible custodian of the samples, and what policies and procedures are in place to do this. These visits also gave the repository and the Project management a chance to listen to, and thus better understand, community members' expressions of hopes for the Project and future research with their samples, as well as lingering concerns.

The Project's Ethical, Legal and Social Implications Group, along with the investigators who collected the samples, continue to explore ways for CAGs in different participating communities to initiate contact with each other (such as through linked websites), and the Coriell Institute has made additional funds available to help support such activities. The hope is that such efforts, over time, will lead to greater transparency and trust, and to the development of a sense of the Project as a truly global enterprise.

## Conclusion

Like all genetic variation research, the HapMap Project raises complex ethical, social and cultural issues. We have tried to address some of these issues, in part, through the processes of community engagement and individual informed consent described in this paper. More time must pass before we can fully reflect on the lessons we have learned. New issues may arise that cannot yet be anticipated – especially as the HapMap and the samples begin to be widely used. The CAGs have only recently been formed and their effectiveness has not yet been tested. Community engagement is still underway in other localities with other populations and, as we have noted, the experiences at those sites may be quite different from those described here.

As with our understanding of the science of genetic variation, our understanding of how to responsibly conduct research aimed at the study of individual and group differences is evolving. We do not claim to have found the perfect model for engaging communities, and indeed, we do not believe that a perfect model exists. We also do not think that exercises in public dialogue alone can substitute for care in research design, data analysis and reporting of the findings of genetic variation studies.

Nor do we mean to suggest that a community engagement process as extensive as that used for this Project must always be undertaken when samples are being collected for genetic research with identified populations. However, the experience of this Project does suggest that, at the least, approaching such research in a spirit of openness can improve the presentation and interpretation of the science, help investigators better understand the attitudes and concerns of the communities whose samples they seek to study and, simultaneously, help communities become engaged in the science.

## Appendix 1

*Community Advisory Groups*

The samples collected for the HapMap Project were not only used for the HapMap Project, but will also be used for future genetic variation studies. Such future studies, by building on the HapMap data, will enhance the usefulness of the HapMap itself. However, the Project recognized that members of the participating communities have a legitimate interest in remaining informed about the nature of these future studies in which their samples will be used.

Thus, in accordance with the policy of the repository at the Coriell Institute, a CAG was established at each site where new samples were collected to serve as a liaison between the community and the repository. Each CAG consists of about 6–8 community representatives (who may or may not themselves be sample donors). The CAGs meet periodically on a schedule of their choosing to discuss any matters of interest or concern, such as the status of the Project, how the HapMap and the samples are being used, or developments in genetic variation research generally. Each CAG is kept informed about general Project developments and future studies that use their community's samples through a periodic newsletter (translated into the language of each participating community) and quarterly reports. The CAGs can then disseminate this information within their broader local communities.

The Coriell Institute will work with the CAGs to resolve any concerns about future uses of the samples as they arise. In the unlikely event that a community's samples were to be used in a manner inconsistent with the community's stated wishes, as documented in the consent forms, the community could ask that all of its samples be withdrawn from further distribution and the Coriell Institute would comply with that request.

## Appendix 2

*Language and Comprehension*

Language and comprehension issues were, as predicted, quite formidable. For example, in the Yoruba language, no word exists for the concept of 'genetics'. Although most Yoruba people speak both Yoruba and English and understand the idea of inheritance (e.g. 'diseases passed down in families from the mother and father to their children'), explaining the meaning of 'SNPs' and 'haplotypes' was quite difficult, especially because almost none of the Yoruba people engaged for participation had formal training in genetics or biology. Even in Tokyo and Beijing, where many discussions were held in university settings, and in the CEPH community, where donors are unusually conversant about genetics due to their long history of involvement in other genetic studies, explaining the Project and the principles of genetic variation research in terms that could easily be understood was challenging.

One contributing factor may have been that the Project is not directly related to the study of any particular disease. While most people seem to understand the idea of looking at blood samples to unravel the genetic component of common diseases, it is much harder to comprehend the purpose of creating a general resource that is not immediately related to the study of a specific, named disease, and for which only blood samples, without identifiers or

medical data, are being collected. This experience underscores the importance of developing robust informed consent and engagement or consultation processes when conducting non-disease-specific genetic variation research. Such activities can be informative in modifying recruitment materials and consent documents to ensure that they are accessible to lay and culturally responsive persons.


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*Clinical Report*

# Mandibuloacral Dysplasia and a Novel *LMNA* Mutation in a Woman With Severe Progressive Skeletal Changes

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A 56-year-old Japanese woman with mandibuloacral dysplasia and type A lipodystrophy is described. Mutation analysis identified a homozygous missense mutation (1585G > A) in exon 9 of the *LMNA* gene that replaces well-conserved residue alanine at position 529 to threonine (A529T). The woman showed, in addition to the usual clinical manifestations of the disorder, severe progressive skeletal changes: osteoporotic changes with multiple fractures; osteolysis of the right radius; and destructive changes of the vertebrae, leading to compression of the cervical spinal cord and paraplegia. Laboratory findings included markedly reduced bone mineral density; significantly increased urine N-telopeptide of collagen type I, an osteoclast marker; and normal serum bone specific alkaline phosphatase, an osteoblast marker. Regular follow up of adult patients with the disorder is desirable, including skeletal radiography, estimates of bone mineral density, and biochemical markers of bone turnover. Treatment with bisphosphonates to inhibit osteoclast activity is likely to be beneficial. © 2007 Wiley-Liss, Inc.

**Key words:** mandibuloacral dysplasia; *LMNA*; osteolysis; destructive vertebral changes; paraplegia; bone mineral density; biochemical markers of bone turnover

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## INTRODUCTION

Mandibuloacral dysplasia (MAD) is a rare autosomal recessive disorder characterized by postnatal growth retardation, craniofacial features (prominent eyes, beaked nose), skeletal manifestations (mandibular and clavicular hypoplasia, acroosteolysis, delayed closure of cranial sutures, and joint contractures), cutaneous changes (atrophic skin, partial alopecia, mottled hyperpigmentation), and partial (type A) or generalized (type B) lipodystrophy [Simha et al., 2003; Afifi and El-Bassyouni, 2005]. A total of 15 patients with MAD and type A lipodystrophy (MADA) from 10 families have been found to have homozygous R527H or A529V missense mutations in the lamin A/C (*LMNA*) gene [Novelli et al., 2002; Shen et al., 2003; Simha et al., 2003; Garg et al., 2005]. The proteins lamin A/C are major components of nuclear lamina, a fibrous network underlying the inner surface of the nuclear envelope that determines nuclear shape and size [Lin and Worman, 1993]. Another patient with MAD and type B lipodystrophy (MADB) has been reported to have compound heterozygous mutations in the zinc metalloproteinase (*ZMPSTE24*) gene, involved in post-translational processing of prelamin A [Agarwal et al., 2003]. Additionally, Garg et al. [2005] reconfirmed other six patients from two families with *LMNA* mutations as having MAD, who were originally reported as

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Hutchinson–Gilford progeria syndrome (HGPS) [Cao and Hegele, 2003; Plasilova et al., 2004], and presented another unpublished patient with MAD and *ZMPSTE24* mutations. HGPS, one of the most emblematic segmental aging disorders, is also caused by *LMNA* mutations [Navaro et al., 2006]; and lamin A is implicated in physiological aging [Scaffidi and Misteli, 2006]. However, there has been little information about manifestations accompanied by aging in patients with molecularly confirmed MAD.

We encountered a 56-year-old Japanese woman with severe skeletal manifestations of MAD and a homozygous A529T mutation of the *LMNA* gene. She is the oldest reported patient with molecularly confirmed MAD. Her detailed history will be presented.

## CLINICAL REPORTS

The 56-year-old woman was born as the sixth of six offspring of healthy consanguineous Japanese parents (cousins). Her oldest brother allegedly had severe short stature, generalized weakness, and a facial appearance similar to the patient. He was a professional doll painter, but could not walk unassisted, and expired in his forties due to total debilitation. The other four siblings were healthy. The woman was short in childhood. She was good at music and art, but she was too weak to participate in hard sports. Around age 13, she attained menarche. After graduating from a dressmaking school, she worked as an excellent tailor and painted many pictures as a hobby.

At age 25 years, she broke her right ulna, which was resected surgically. She had recurrent dislocations of the left shoulder, was treated with manual reduction, and once had a fracture of the right shoulder. She noticed shortening of the right forearm in her mid-30s without pain. She lost all her teeth in her mid-20s to mid-30s. At age 47 years, uterine myoma was treated with a LHRH analog, followed by cessation of menstruation. At age 53 years, she fell and broke her right femur, which was corrected surgically. After the surgery, she could walk unassisted.

At age 56 years, she developed paraplegia, and was referred to us. Her height was 134 cm (−4.8 SD) and weight 24 kg (−3.8 SD). She had a progenoid appearance. (She declined having photos taken and published.) Her scalp hair was sparse and the fontanel was open. She had prominent eyes with down-slanting palpebral fissures; a pinched nose with hypoplastic alae nasi and inverted nostrils; a bulbous cheek, and micrognathia. Narrow, drooping shoulders and lack of breast development were noted. The terminal phalanges of her fingers and toes were short and club-shaped (Fig. 1A,B). The phalangeal joints were rigid. Her right forearm was soft and shortened. The skin on the limbs was thin

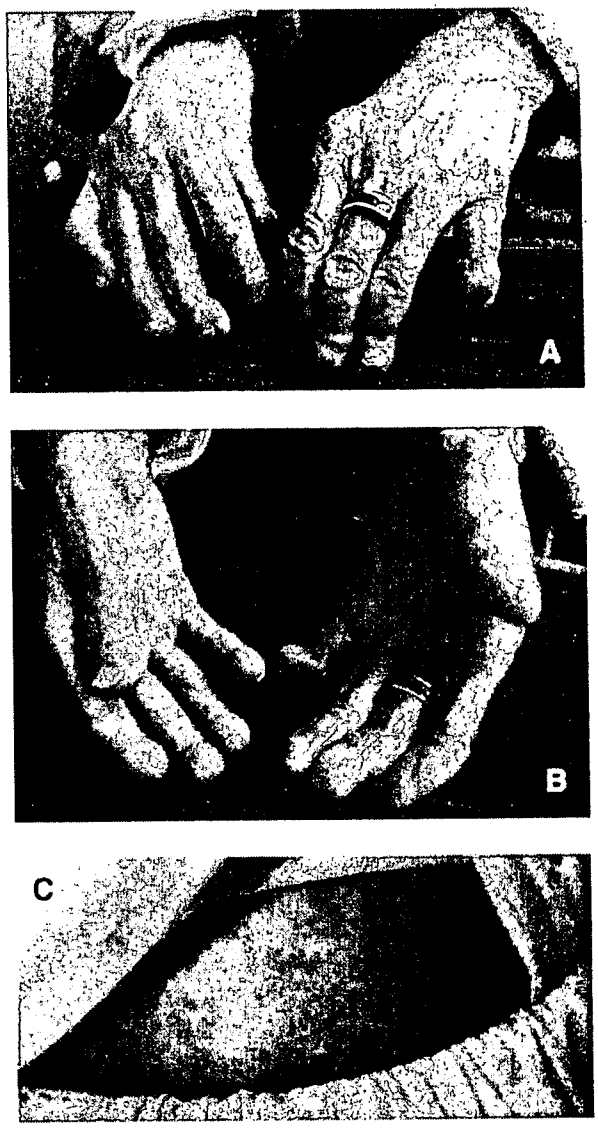


FIG. 1. Photographs of the patient at age 56 years. **A,B**: Hands. **C**: Skin of the abdomen. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

and atrophic (Fig. 1A,B), whereas it was thicker on the trunk with mottled pigmentation (Fig. 1C). She showed marked loss of subcutaneous fat in the limbs and slight excess in the truncal regions (type A lipodystrophy) (Fig. 1A–C). Serum levels of calcium, phosphorus, alkaline-phosphatase were all normal at 9.4, 4.6, and 333 IU/L, respectively. Serum creatinine and creatine phosphokinase levels were reduced at 0.37 mg/dl and 23 IU/L, suggesting poor muscle volume. Serum level of intact parathyroid hormone was normal at 18.3 pg/ml (range, 10–65) and that of 1,25-$(OH)_2$-vitamin D was increased at 91.1 pg/ml (range, 20–60). N-telopeptide of collagen type I (NTX), an osteoclast marker, was markedly increased in urine at 247.6 nmol/mmol creatinine (range for postmenopausal females, 14.3–89.0);

whereas bone specific alkaline phosphatase (BAP), an osteoblast marker, in serum was normal at 35.0 U/L (range, 9.6–35.4). Fasting glucose level of 96 mg/dl, IRI (immunoreactive insulin) level of 5.2 μU/ml, and accordingly HOMA-R (homeostasis model assessment) of 1.23 all indicated insulin resistance unlikely. Hemoglobin $A_{1C}$ was 5.7% (range, 4.3–5.8).

## RADIOLOGICAL EXAMINATIONS

Radiographs and CT scans of the skull showed thinning of the cranial bone, widened sutures, and delayed closure of fontanels (Fig. 2A–D). Radiographs of the upper limbs showed acroosteolysis of the distal phalanges, osteolysis of the right radius, cortical thinning of the long bones, and multiple calcification around osteolytic lesions (Fig. 2E,F). A chest X-ray showed a bell-shaped thorax, aplasia of bilateral clavicles with irregular calcifications, and a round tumor (Fig. 2G). MRI indicated the tumor to be localized at the posterior mediastinum, attached to the spine, suggesting it to be neurinoma or ganglioneuroma. Radiographs of the spine showed cortical thinning of the vertebrae; destructive changes of the cervical and lumbar vertebrae with multiple calcifications, leading to cervical kyphosis and lumbar lordosis; and thoracic scoliosis (Fig. 2H, I, and K–N). MRI revealed compression of the spinal cord due to destructive kyphosis of the cervical spine (Fig. 2J). A radiograph of the pelvis showed cortical thinning of the pelvic bones and the femora, and multiple calcifications (Fig. 2O). Bone mineral density, measured with dual energy X-ray absorptiometry of the lumbar spine, was markedly reduced at 0.500 g/cm$^2$ ($Z$ score −2.6).

## MUTATION ANALYSIS

After obtaining appropriate informed consent, leukocyte genomic DNA was amplified by polymerase chain reaction (PCR) for the 12 exons and exon–intron boundaries of the *LMNA* gene. The primer sequences were as described previously [Brown et al., 2001]. PCR was performed with AmpliTaq Gold (Applied Biosystems, Foster City, CA) for 30 cycles consisting of 30 sec at 94°C, 30 sec at 60°C, and 30 sec at 72°C. After purification on Centri-Sep spin columns (Applied Biosystems), the PCR products

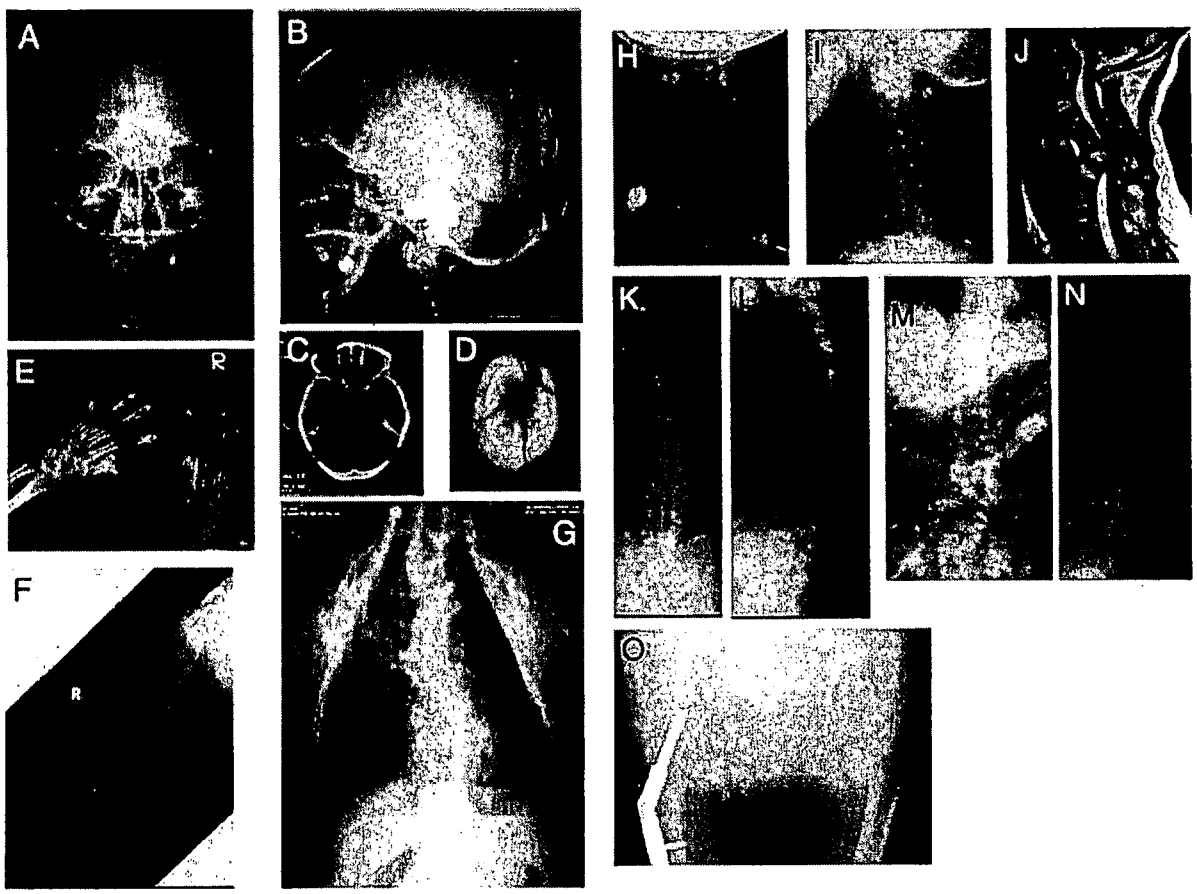


Fig. 2. Radiological examinations of the patient at age 56 years. **A,B,E–I,K–O**: Skeletal radiographs. **C,D**: CT scans of the skull. **J**: MRI of the cervical spine.

were directly sequenced using the ABI Big Dye terminator mix (Applied Biosystems) and forward or reverse primers used for amplification. Reactions were run on an ABI 3100 automated sequencing analyzer (Applied Biosystems). Data were analyzed using Sequencher 4.1.2 software (Gene Codes, Ann Arbor, MI).

A homozygous G → A transition was identified at nucleotide position 1585 (1585G > A) in exon 9 (Fig. 3), which resulted in an alanine to threonine substitution at amino acid position 529 (A529T).

## DISCUSSION

The disorder in the woman we have described was diagnosed clinically as MADA because of the combination of postnatal growth retardation; typical craniofacial, skeletal, and cutaneous features; and type A lipodystrophy. Parental consanguinity and a similarly affected brother were compatible with autosomal recessive inheritance. In addition to cardinal features of MADA, she showed severe progressive skeletal changes: osteoporotic changes with multiple fractures, osteolysis of the right radius, and destructive changes of the vertebrae, leading to paraplegia.

Analysis in the woman identified a homozygous missense mutation (1585G > A) of the *LMNA* gene, leading to alanine to threonine conversion at codon 529 (A529T). Garg et al. [2005] reported a male and a female patient with MADA who belonged to two pedigrees from Turkey, both with a homozygous missense mutation (A529V due to 1586C > T) involving the same codon as that implicated in the woman we described. The alanine residue at codon 529 is well conserved across many species, such as rat, mouse, chicken, and Xenopus laevis [Garg et al., 2005].

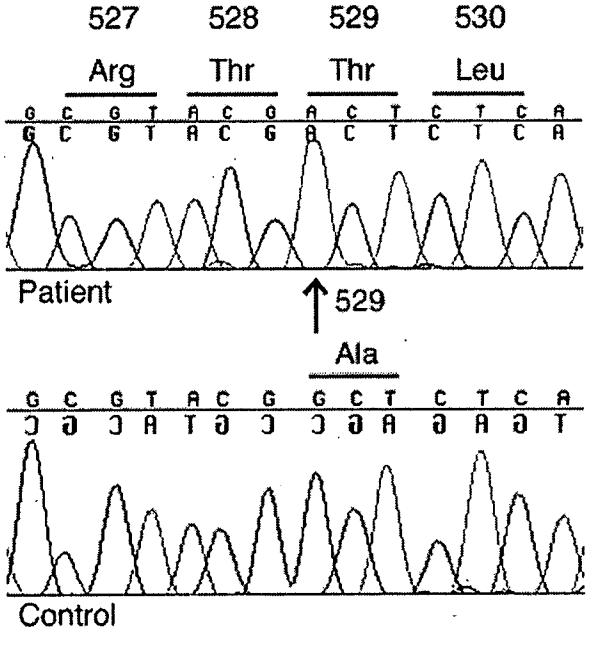


FIG. 3. Direct sequencing of *LMNA* showing the G → A transition which resulted in alanine to threonine substitution at amino acid position 529. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

To date, a total of 22 patients have been reported to have MAD and *LMNA* or *ZMPSTE24* mutations (Table I) [Schrander-Stumpel et al., 1992; Tudisco et al., 2000; Novelli et al., 2002; Agarwal et al., 2003; Cao and Hegele, 2003; Cogulu et al., 2003; Shen et al., 2003; Simha et al., 2003; Plasilova et al., 2004; Garg et al., 2005]. They ranged in age from four to 37 years, were originally diagnosed as MAD (17 patients from 12 families) or HGPS (5 patients from 2 families); and together had four different homozygous or compound heterozygous *LMNA* mutations and two compound heterozygous *ZMPSTE24* mutations. A 21-year-old woman with a homozygous A529V *LMNA* mutation lacked breast development, although she attained menarche at age 10 and had regular menstruation cycle [Cogulu et al., 2003; Garg et al., 2005]. The woman we described with a homozygous A529T *LMNA* mutation and menarche at age 13 also lacked breast development. It could be that a missense *LMNA* mutation at codon 529 is related to absent breast development. According to the growth data, it seems that the patients with missense *LMNA* mutations at position 529 and 542 are more severely stunted than those with position 527 *LMNA* or *ZMPSTE24* mutations.

The 56-year-old woman we described suffered from severe progressive skeletal changes, including severe osteoporotic changes with multiple fractures, osteolysis of the right radius, and destructive changes of the vertebrae. She had a marked increase in osteoclast activity with normal osteoblast activity, as evidenced by measurement of NTX and BAP, biochemical markers of bone turnover; and had reduced bone mineral density. Four factors may be responsible for the development of these skeletal changes. First, her genotype (a homozygous A529T substitution of *LMNA*) might be related to marked skeletal fragility. A 28-year-old woman with a compound heterozygous *LMNA* mutation (R471C/R527C) was also reported to have severe osteoporosis with multiple fractures [Cao and Hegele, 2003]. Second, postmenopausal state induced by a LHRH analog at 47 years of age could have had an osteoporotic effect. The woman received no treatment to prevent osteoporosis. She had a fracture of the right femur 6 years after the initiation of a LHRH analog, and multiple fractures of the vertebrae an additional 3 years later. Third, severe osteolysis of the right radius might be derived from long-term hard use of the right arm as a tailor and overload on the right radius due to previous fracture and resection of the right ulna. Last, aging could have accelerated

TABLE I. Published Patients with Molecularly Identified MAD

| Patient | Family | Age | Sex | Origin | Mutation | Height | Lipodystrophy | Specific clinical features | References |
|---|---|---|---|---|---|---|---|---|---|
| MAD patients with *LMNA* mutations | | | | | | | | | |
| 1 | 1 | 33y | M | Italian | 1580G > A, R527H | 161 cm (<3rd centile) | A | | Tudisco et al. [2000], Novelli et al. [2002] |
| 2–3 | 2 | | F, F | Italian | 1580G > A, R527H | | A | | Novelli et al. [2002] |
| 4–6 | 3 | | M, F, M | Italian | 1580G > A, R527H | | A | | Novelli et al. [2002] |
| 7 | 4 | | F | Italian | 1580G > A, R527H | | A | | Novelli et al. [2002] |
| 8, 9 | 5 | | M, M | Italian | 1580G > A, R527H | | A | | Novelli et al. [2002] |
| 10 | 6 | 20y | F | Mexican | 1580G > A, R527H | Growth retardation (+) | A | | Simha et al. [2003] |
| 11 | 6 | 16y | F | Mexican | 1580G > A, R527H | Growth retardation (+) | A | | Simha et al. [2003] |
| 12 | 7 | 12y | M | Italian | 1580G > A, R527H | Growth retardation (−) | A | | Simha et al. [2003] |
| 13 | 8 | 12y | M | Mexican | 1580G > A, R527H | 5th–10th centiles | A | | Shen et al. [2003] |
| 14 | 9 | 18y | M | Turkish | 1586C > T, A529V | 144 cm (<3rd centile) | A | Atrial septal defect | Garg et al. [2005] |
| 15 | 10 | 21y | F | Turkish | 1586C > T, A529V | 137 cm (<3rd centile) | A | Absent breast development | Cogulu et al. [2003]; Garg et al. [2005] |
| 16 | 11 | 56y | F | Japanese | 1585G > A, A529T | 134 cm (−4.8 SD) | A | Absent breast development, osteoporotic changes with multiple fractures, osteolysis of the radius, destructive vertebral changes leading to paraplagia | Present report |
| MAD patients with *LMNA* mutations originally diagnosed as HGPS | | | | | | | | | |
| 17 | 12 | 28y | F | Caucasian | 1411C > T/ 1579C > T, R471C/R527C | | NA | Severe osteoporosis with multiple fractures | Cao and Hegele [2003] |
| 18 | 13 | 4y | M | Indian | 1626G > C, K542N | 96 cm (−3.0 SD) | B | | Plasilova et al. [2004] |
| 19 | 13 | 10y | F | Indian | 1626G > C, K542N | 95 cm (−7.7 SD) | B | Absent sexual maturation, died at age 10 years (pneumonia) | Plasilova et al. [2004] |
| 20 | 13 | 15y | M | Indian | 1626G > C, K542N | 124 cm (−5.1 SD) | B | Impaired sexual maturation | Plasilova et al. [2004] |
| 21 | 13 | 17y | F | Indian | 1626G > C, K542N | 120 cm (−12 SD) | B | Absent sexual maturation | Plasilova et al. [2004] |
| MAD patients with *ZMPSTE24* mutations | | | | | | | | | |
| 22 | 14 | 24 | F | Belgian | 1018T > C/1085insT, W340R/ F361fsX379 | 154 cm (3rd–25th centile) at age 16 years | B | Subcutateous calcified nodules, hypermetropia, scarse secondary sexural maturation, progressive glomerulopathy leading to death at age 24 years | Schrander-Stumpel et al. [1992]; Agarwal et al. [2003] |
| 23 | 15 | 37 | M | | N265S/F361fsX379 | | B | Died at age 37 years | Garg et al. [2005] |

y, years; M, male; F, female; A, type A (partial); B, type B (generalized); NA, information not available.

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osteoporosis. Recent analysis of fibroblasts from MAD patients with a homozygous R527H *LMNA* mutation showed accumulation of unprocessed prelamin A, a marked alteration of the nuclear architecture, and chromatin disorganization; and that both accumulation of unprocessed prelamin A and chromatin defects became more severe in older patients [Filesi et al., 2005].

In conclusion, we described a woman with MADA, a A529T *LMNA* mutation, and severe progressive skeletal changes. It is desirable to regularly examine radiographs, bone mineral density, and biochemical markers of bone turnover in adult MAD patients. Treatment with bisphosphonates to inhibit osteoclast activity is likely to be beneficial in preventing pathological fractures.

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ヒトゲノム・再生医療等研究事業

# ゲノムリテラシー向上のための人材育成と教育ツール開発に関する研究

平成19年度　総括研究報告書

研究成果の刊行物・別刷　分冊３／３（雑誌和文）

主任研究者　福嶋　義光

平成20(2008)年3月

## 研究成果の別刷り（雑誌和文）一覧

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# 遺伝学的検査実施時のガイドライン

*Guidelines for genetic testing*

診断の指針 / 治療の指針

福嶋 義光
*FUKUSHIMA Yoshimitsu*

1. 遺伝学的検査(genetic testing)に関連する用語の整理

遺伝学的検査に関連する用語には，「遺伝子検査」，「遺伝子診断」，「DNA 検査」，「核酸検査」などさまざまなものがあり，混乱が生じている．現在，表1のように整理することが提唱されている[1)]．表1の2)遺伝子検査(gene-based testing)と3)核酸検査(nucleic acid-based testing)に関しては，よりよい医療の提供のために行われる検査であり，通常の臨床検査と同様の倫理的取組みを行っていればとくに問題は生じない．一方，1)の遺伝学的検査(genetic testing)は一生変化しない情報，将来を予見しうる情報，血縁者も関与しうる情報である遺伝情報を明らかにする検査であり，通常の医療情報とは異なる側面があるため，慎重な取扱いが求められており，各種ガイドラインが制定されている．

2. 厚生労働省「医療・介護関係事業者における個人情報の適切な取扱いのためのガイドライン」
<http://www.mhlw.go.jp/shingi/2004/12/s1224-11.html>

個人情報保護法が2005年4月に完全施行となることを受けて，厚生労働省は「医療・介護関係事業者における個人情報の適切な取扱いのためのガイドライン」を作成した．個人情報の中でも遺伝情報は特殊であることから，ガイドラインの10番目の項目に「遺伝情報を診療に活用する場合の取扱い」を設け，「医療機関等が，遺伝学的検査を行う場合には，臨床遺伝学の専門的知識を持ち，本人及び家族等の心理社会的支援を行うことができる者により，遺伝カウンセリングを実施する必要がある」と記載している(表2)．

3. 遺伝医学関連10学会「遺伝学的検査に関するガイドライン」(日本遺伝カウンセリング学会，日本遺伝子診療学会，日本産科婦人科学会，日本小児遺伝学会，日本人類遺伝学会，日本先天異常学会，日本先天代謝異常学会，日本マススクリーニング学会，日本臨床検査医学会(以上五十音順)，家族性腫瘍研究会)
<http://jshg.jp/>

2)の厚生労働省のガイドラインでは診療の場で用いられる遺伝情報の扱い方の原則のみを示しているが，具体的には厚生労働省のガイドラインにも正式に引用されている本ガイドラインを参照すべきである．

本ガイドラインでは最初に総論として，Ⅰ．本ガイドラインの対象，Ⅱ．遺伝学的検査の実施，Ⅲ．遺伝学的検査の結果の開示，Ⅳ．遺伝学的検査と遺伝カウンセリングの記載があり，そのあとに各論として，Ⅴ．目的に応じた遺伝学的検査における留意点の項が設けられ，遺伝学的検査が考慮される6つの場面(1．発症者を対象とする遺伝学的検査，2．保因者の判定を目的とする遺伝学的検査，3．発症予測を目的とする遺伝学的検査[発症前検査および易罹患性検査]，4．薬物に対する反応性の個体差を判定することを目的とする遺伝学的検査，5．出生前検査と出生前診断，6．新生児マススクリーニング検査)における留意点が詳細に記載されている．

表1 遺伝学的検査に関係する用語の整理

1)「遺伝学的検査(genetic testing)」
遺伝病の遺伝子検査など，一生変化しない遺伝情報(生殖細胞系列遺伝子解析)を明らかにする検査．遺伝学的検査の目的には確定診断のための検査，保因者検査，発症前検査，易罹病性検査，薬理遺伝学的検査，出生前検査，新生児スクリーニングなどが含まれる．

2)「遺伝子検査」(gene-based testing)
癌細胞のDNA検査，遺伝子発現解析など，病状とともに変化する一時的な遺伝情報を明らかにする検査(体細胞遺伝子解析，遺伝子発現解析)．体の中に癌細胞があるかどうかを調べたり，採取した腫瘍細胞の悪性度を明らかにするなどの目的で行われる．

3)「核酸検査」(nucleic acid-based testing)
感染症のDNA検査，RNA検査などヒト以外の遺伝情報を明らかにする検査．培養困難な病原微生物の同定検査，抗生物質加療中や感染初期の病原微生物の検出，移行抗体が疑われた際の抗原検出，病原微生物の感染源調査などを目的として行われる．

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Key words　遺伝学的検査に関するガイドライン　遺伝カウンセリング　臨床遺伝専門医　全国遺伝子医療部門連絡会議

0371-1900/07/¥50/頁/JCLS



表2 医療・介護関係事業者における個人情報の適切な取扱いのためのガイドライン
(厚生労働省　平成16年12月24日告示)

10. 遺伝情報を診療に活用する場合の取扱い
遺伝学的検査等により得られた遺伝情報については，遺伝子・染色体の変化に基づく本人の体質，疾病の発症等に関する情報が含まれるほか，生涯変化しない情報であること，またその血縁者に関わる情報でもあることから，これが漏えいした場合には，本人及び血縁者が被る被害及び苦痛は大きなものとなるおそれがある．したがって，検査結果及び血液等の試料の取扱いについては，UNESCO国際宣言，医学研究分野の関連指針及び関連団体等が定めるガイドラインを参考とし，とくに留意する必要がある．
また，検査の実施に同意している場合においても，その検査結果が示す意味を正確に理解することが困難であったり，疾病の将来予測性に対してどのように対処すればよいかなど，本人及び家族等が大きな不安を持つ場合が多い．したがって，医療機関等が，遺伝学的検査を行う場合には，臨床遺伝学の専門的知識を持ち，本人及び家族等の心理社会的支援を行うことができる者により，遺伝カウンセリングを実施する必要がある．

4. 遺伝カウンセリングの重要性

上記2つのガイドラインにおいて，遺伝学的検査を行う場合には，遺伝カウンセリングが必須であることが述べられている．遺伝カウンセリングとは，遺伝性疾患の患者・家族またはその可能性のある人(クライエント)に対して，生活設計上の選択を自らの意思で決定し行動できるよう臨床遺伝学的診断を行い，医学的判断に基づき適切な情報を提供し，支援する医療行為である．遺伝カウンセリングにおいてはクライエントと遺伝カウンセリング担当者との良好な信頼関係に基づき，さまざまなコミュニケーションが行われ，この過程で心理的精神的援助がなされる．遺伝カウンセリングは決して一方的な遺伝医学的情報提供だけではないことに留意すべきである．わが国では，発端者の診断・治療にあたっている主治医がさまざまな遺伝に関する情報提供を患者・家族に行っていると考えられるが，遺伝カウンセリングでは単なる情報提供だけではなく心理的・精神的・社会的サポートを行うことがきわめて重要である．遺伝カウンセリングを含む遺伝医療を担う人材育成のために，日本人類遺伝学会と日本遺伝カウンセリング学会では協同して「臨床遺伝専門医」<http://www.jshg.jp/>を養成しており，2005年度までに，599名を認定している．遺伝学的検査を円滑に実施するためには，臓器ごとの専門分野だけの知識ではなく幅広い遺伝医学の知識を身に付け，遺伝情報の特殊性と倫理的問題を理解しておく必要があり，御自身で臨床遺伝専門医となるか，あるいは臨床遺伝専門医と連携をとることが望まれる．

5. 全国遺伝子医療部門連絡会議

各種ガイドラインの影響もあり，すでに大学病院を中心とする特定機能病院ではそのほとんどに遺伝子医療部門が設立されていることが厚生労働科研「遺伝子医療の基盤整備に関する研究班」の調査で明らかにされ，2003年から全国遺伝子医療部門連絡会議が行われている．第1回(2003年)には52，第2回(2004年)には81，第3回(2005年)には97の大学病院・国立医療機関等から代表者が集い，遺伝子医療の実践に関連して，遺伝カウンセリングの位置づけ，組織作り，担当者，診療費，診療録の問題など，各施設間の情報交換，意見交換を行い，わが国の遺伝医療のあり方について検討している．(連絡会議の詳細な報告書が信州大学医学部附属病院遺伝子診療部のホームページ<http://genetopia.md.shinshu-u.ac.jp/genetopia/index.htm>に掲載されているので，是非御参照いただきたい)．

文　献
1) 福嶋義光：序文(日本臨床増刊号：遺伝子診療学－遺伝子診断の進歩と遺伝子治療の展望－)．日本臨床　63(増刊号12)：1-4，2005.
2) 福嶋義光：総論　－遺伝子診断の定義・分類および倫理指針・ガイドライン(連載1「遺伝子診断の最前線」)．医学の歩み　212：1086-1090，2005.

# 遺伝学的検査に関する注意点

涌井敬子[*1]・福嶋義光[*2]

はじめに

ヒトゲノム・遺伝子解析研究の進展により，2003年にはヒトのもつ約30億塩基対の塩基配列の一次構造が決定された．原因不明であったさまざまな疾患の責任遺伝子や発症のメカニズムが分子レベルで次々に明らかにされ，責任遺伝子の明らかになった単一遺伝子疾患については遺伝子診断が新たな臨床診断法として診療に用いられつつあり，さらに原因に基づく病態の解明や治療へ向けての研究が進められている．

近年では稀な遺伝性疾患だけでなく，誰にでもなじみのある，高血圧，糖尿病，心筋梗塞などの多因子遺伝疾患や癌も，個々人の遺伝要因が関与していることが明らかになってきた．さらに，一部の治療薬については，個々人の遺伝子多型と薬物反応性の関連が証明され，効果・副作用の判定や適切な投与量決定のために遺伝学的検査が用いられようとしている．あらゆる健康の問題に遺伝要因が関係しているということで，将来は個々人の薬物反応性・疾患感受性などの，いわゆる体質の違いを考慮に入れたオーダーメイド医療が導入され，遺伝学的検査の役割がますます大きくなることが予想される．

本稿では“遺伝学的検査”についての定義と，実施に際して求められる注意点やその理由などを正確に理解していただければ幸いである．

## 遺伝性疾患とは？

“遺伝学的検査”についての解説の前に，まず，よく誤解されている“遺伝性疾患”について解説する．遺伝性疾患(genetic disease)とは，生まれながらに有している染色体や遺伝子(gene)といった遺伝要因が発症に関係している病気のことをいい，必ずしも遺伝する(inherited)病気と同意語ではない．親に遺伝子変異がなくても，配偶子形成期に生じた遺伝子変異(突然変異)をもつ配偶子がたまたま受精することにより遺伝性疾患の個体が発生する場合もある．生まれながらにあるいは小児期までに症状が現れる常染色体優性遺伝性疾患の多くは突然変異が原因である．また，人は皆，なんらかの遺伝子変異を有しており，将来，遅発性の遺伝性疾患を発症する可能性は否定できない．すべての人はなんらかの劣性遺伝病の保因者であり，さらに，誰でも突然変異による遺伝子変異や染色体異常を伴った配偶子(卵子や精子)をある頻度で有している．誰にでも遺伝性疾患の子どもが生まれる可能性があるのである．

## ヒト遺伝情報の特殊性とガイドライン

UNESCO(United Nations Educational, Scientific and Cultural Organization；国際連合教育科学文化機構)は，ヒトの遺伝情報のもつ重要性に鑑み，その扱いについて以下のような“ヒト遺伝情報に関する国際宣言”を採択した．「ヒト遺伝情報は，①個人に関する遺伝的易罹病性を予見しうること，②世代を超えて，子孫を含めた家族，集団に対して重大な影響を与え得ること，③試料収集の時点では必ずしも明らかにはされていない情報を含み得ること，④個人または集団に対する文化的な重要性を有し得ること，の理由により，特別な地位が与えられるべきであり，したがって，ヒト遺伝情報は，a)医療，b)研究，c)法的措置など，に限って用いられるべきであり，健康にかかわる重要な意味をもつ可能性がある遺伝学的検査を行う場合には，当事者が遺伝カウンセリングを適切な方法で受けられるようにすべきである．」

わが国においては，2005年4月から実施された“個人情報保護法”に伴って，上記のUNESCO国際宣言の趣旨を盛り込んで策定あるいは改訂された，国が定めた遺伝情報にかかわる三つのガイドラインがある．厚生労働省から告示された「医療・介護関係事業者における個人情報の適切な取扱いのためのガイドライン」，3省(文部科学省，厚生労働省，経済産業省)から告示された「ヒトゲノム・遺伝子解析研究に関する倫理指針」，経済産業省から告示された「経済産業分野のうち個人遺伝情報を用いた事業分野における個人情報保護ガイドライン」の三つである．また，遺伝学的検査については，遺伝医学関連10学会が「遺伝学的検査に関するガイドライン」に配慮すべき事項を詳細に記載，日本衛生検査所協会が「ヒト遺伝子検査受託に関する倫理指針」として遺伝学的検査の受託に際しての遵守事項を定めた．本稿で各々について詳細に説明するスペースはないが，遺伝学的検査にかかわる者は原文(webサイト後述)を熟読されたい．

## 遺伝学的検査とは？

遺伝学的検査(genetic testing)とは遺伝性疾患を診断する目的で，ヒトのDNA，RNA，染色体，タンパク質(ペプチド)，代謝産物を解析もしくは測定することである．この目的には確定診断のための検査，保因者検査，発症前検査，易罹患性検査，薬理遺伝学的検査，出生前検査，新生児スクリーニングなどが含まれる．通常，純粋に研究目的で行われるヒトゲノム・遺伝子解析や生化学的解析，細胞病理学的解析，および法医学的検査は含まない[遺伝学的検査に関するガイドライン(2003)より]．すなわち，遺伝学的検査は，a)ヒトが生まれながらに有している病気や体質と関連のある生殖細胞系列変異[注]すなわち遺伝子や染色体などの遺伝情報の変化を明らかにしようとする検査であり，b)検査方法には，遺伝子検査，染色体検査，遺伝生化学的検査などがあり，c)その適応としては，①先天性の染色体異常症や，原因の同定された既知の遺伝性疾患(奇形症候群，先天代謝異常症，骨系統疾患，神経変性疾患，家族性腫瘍など)の診断，②習慣流産や不妊症など生殖障害の原因検索，③責任遺伝子変異の特定された常染色体優性遺伝性疾患(神経変性疾患，家族性腫瘍など)の発症前診断，④責任遺伝子変異の特定された劣性遺伝性疾患(代謝異常症など)の保因者診断，⑤親の染色体均衡型構造異常や遺伝子変異が同定された重篤な遺伝性疾患の家系の出生前診断など，が挙げられる．

細菌・ウイルスなどの病原体の遺伝子検査は，感染症の原因の特定，治療法の選択やその効果の確認を目的に臨床検査として行われるもので，生体試料を扱うが検出のターゲットは外来の微生物であり，倫理的問題はなく通常の臨床検査として扱われ遺伝学的検査には含めない．また，癌はヒトの体の細胞の一部に起こる遺伝子変異・遺伝子発現・染色体異常が原因であることが明らかになってきたが，変異は肝臓や大腸といった臓器や骨髄細胞など，各細胞に分化した後の細胞の一部に限局して後天的に起こる体細胞変異[注]である．癌の遺伝子検査や染色体検査は，正常な細胞には認めない癌細胞に特異的な変異の有無を調べるもので，その変異は次世代に受け継がれないので厳密には遺伝学的検査には含めない．ただし，染色体については，生まれながらにある染色体に変化を有しているヒトもおり(均衡型転座など)，そういった場合にはターゲットとする癌細胞にのみ特異的に起こった変化だけでなく，生殖細胞系列の変異をも同時に検出されることになる．したがって，癌の病型分類や治療法の選択を目的として行われる染色体検査であっても，初めて実施する際にはそのことにも留意して検査前遺伝カウンセリングを実施し，万が一，先天的と考えられる異常を見いだした場合には，染色体異常症に精通した臨床遺伝の専門家に紹介することが望ましい．

[注]生殖細胞系列変異(germline mutation)と体細胞変異(somatic mutation)：
遺伝子変異には生殖細胞系列変異と体細胞変異がある．生殖細胞系列の変異とはその個体が形成される基となった精子あるいは卵子(生殖細胞，配偶子)の段階で，既にその変異が存在している，すなわち受精卵の段階で存在している遺伝子変異のことであり，その個体を形成するすべての細胞に共通して存在している．生殖細胞系列の変異は生涯変化することがなく，また，血縁者とも共有している可能性があるという特殊性がある．一方，体細胞変異とは体の細胞のごく一部の細胞だけに後天的に生じた変異である．癌細胞にみられる変異がその代表である．検査には変異をもつ細胞(癌細胞など)を用いる必要があり，それ以外の細胞には体細胞変異は存在せず，次世代に受け継がれることも，血縁者が共有しているということもない．


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## 遺伝学的検査実施に際しての留意点

医療の現場で診療目的に行われる遺伝情報の取り扱いについて国(厚生労働省)が示した初めての指針である「医療・介護関係事業者における個人情報の適切な取扱いのためのガイドライン」のなかで,「UNESCO国際宣言や医学研究分野の関連指針及び関連団体等が定める指針(＊筆者注:“遺伝学的検査に関するガイドライン”が該当)等を参考とし,臨床遺伝学の専門的知識を持ち,本人及び家族等の心理社会的支援を行うことができる者により,遺伝カウンセリングを実施する必要がある」と明記された.

遺伝学的検査を行う際の具体的留意点としては,①検査を実施する場合には検査の有用性,分析的妥当性(確立された検査法,適切な精度管理の実施),臨床的妥当性(感度,特異度,陽性的中率の確認),臨床的有用性が確認できていること(臨床的有用性の確立していない遺伝学的検査実施は禁止),②検査前の説明,検査結果告知,フォローアップを含め,遺伝カウンセリングの一環として実施されなければならないこと,③専門の異なる複数の医師とコ・メディカルのメンバーを含めたチーム医療でおこなう総合的臨床遺伝医療の中で行われる必要があることなどが挙げられている[“遺伝学的検査に関するガイドライン”より].さらに,病院内においては,遺伝医療として行われた遺伝子検査・染色体検査の結果を含めた遺伝カウンセリングに関する診療録は,通常の診療録とは別にアクセス権限を限定した施錠できる独立したロッカーに保管することが望ましいとされている.

また,特に商業ベースのほか施設に遺伝学的検査を依頼する際の注意事項としては,依頼書および検体には連結可能匿名化された匿名化IDを記して,本名や生年月日など個人情報に該当する項目は検査に支障のないかぎり記載しないことが望ましいとされるようになってきた.最近では,遺伝学的検査については,遺伝カウンセリングの実施とインフォームド・コンセントの取得を条件として,遺伝子医療体制の整っている施設に限り契約する検査センターもでてきた.染色体検査は保険適用になっている検査で,これまでは通常の臨床検査と同様に扱われてきたが,上記のような対応が求められるようになってきたことを周知願いたい.

## 遺伝カウンセリングとは?

遺伝学的検査の実施に当たってキーワードとしてたびたび登場している“遺伝カウンセリング”についても解説しておきたい.遺伝カウンセリングとは,遺伝性疾患の患者・家族またはその可能性のある人(クライエント)に対して,生活設計上の選択を自らの意思で決定し行動できるよう臨床遺伝学的診断を行い,遺伝医学的判断に基づき遺伝予後などの適切な情報を提供し,支援する医療行為である.遺伝カウンセリングにおいてはクライエントと遺伝カウンセリング担当者との良好な信頼関係に基づき,さまざまなコミュニケーションが行われ,この過程で心理的精神的援助がなされる.遺伝カウンセリングは決して一方的な遺伝医学的情報提供だけではない.わが国では,国が定めた遺伝子解析関連のガイドラインとしては(現在は2004年に改訂されたものが運用されているが)“ヒトゲノム・遺伝子解析研究に関する倫理指針(2001)”が先にできたという経緯から,“遺伝子解析研究のために遺伝カウンセリングを行う”と誤解している人が少なくない.遺伝学的検査は,遺伝医療を必要とするクライエントあるいはその家族に対して医療上のメリットがある場合などに限ってオプションとして示される検査である.臨床検査として確立していない遺伝子解析が勧められる場合もあるが,その場合は「ヒトゲノム・遺伝子解析研究に関する倫理指針」を遵守し,あくまでも研究協力として,目的の研究について倫理委員会の承認を得た後に,クライエントのインフォームド・コンセントを得て行われなければならない.

## 遺伝医療体制整備の必要性

究極の個人情報ともいえる個々人の遺伝情報に対しては,あるべき体制についてのガイドラインが策定されたとはいうものの,遺伝医療体制の整備に関しては,遺伝カウンセリングや遺伝学的検査にかかる費用の問題をはじめとする課題が山積している.また,研究として行われていた遺伝子検査をいつどのような過程を経て臨床検査に移行できるのか,監査する公的な第三者機関もない状況で確認できていることが必須とされている検査の有用性・分析的妥当性・臨床的妥当性・臨床的有用性は,誰がどのようにして確認して認定するのか,実施施設の認定基準をどう定めどう監視するのか,実施施設がガイドラインを遵守しているのか精度管理を適切に行っているのかといったことをどう確認するのか,といった技術的な精度の監視体制の整備も早急に進められる必要があると考える.

## おわりに

最後に,遺伝学的検査は,遺伝子医療体制の整った施設における包括的な診療システムのなかで十分な倫理的配慮をもって取り扱われるべきであることを強調したい.

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原著—探索的研究

# グループワークを中心とした医学科・保健学科合同新入生ゼミナールの実施

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要旨：近年の医療ではチーム医療の重要性がこれまで以上に認識されているが，医学教育の枠組みの中で専攻の異なる学生が一緒に学ぶ機会はほとんどない．そこで医学部内の学科間，専攻間の垣根を取り払って新入生をグループ分けし，チュートリアルに準じた形で自学自習やグループ討論を行う新入生ゼミナールを実施した．
1) 信州大学医学部医学科および保健学科の1年生（約240名）を20のグループに分けて，グループワークと合同講義を行った．各グループはすべての専攻科の学生が加わるように編成した．
2) 医療とコミュニケーションに関する資料を提示し，それをもとにグループごとにテーマ（キーワード）を決めて調査，討論をし，学んだ内容と考察を全体討論会で発表させた．
3) 実習終了後の学生に対するアンケート調査では合同演習により他専攻の学生と交流できたことを高く評価していた一方で，演習時間の少なさやグループの人数の多さに対する不満がみられた．
4) 教員に対するアンケート調査では，実習内容は適切であるもののグループの学生数の多さが問題点としてあげられた．また教員数の確保，演習室の確保，教員の意思統一の点で課題が残った．
5) 本演習は他職種の業務を知り，医療におけるコミュニケーションの重要さを理解する方法として有用であった．一方で自学自習の習慣を身につけるという目標到達には改善の余地が残された．
キーワード：チュートリアル教育，問題志向型学習，コミュニケーション

**Interdisciplinary Freshman Seminar for Health Science Students**

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The importance of cooperation among the staffs of various medical specialties has been recognized. However, medical students have little chance to study with students of other specialties. We planned and held an interdisciplinary freshman seminar based on problem-based group learning for health science students.
1) All freshmen entering the Shinshu University School of Medicine were divided into 20 groups and participated in a group-learning program.
2) Students watched video material focusing on medical communication and were asked to investigate and discuss this issue in greater detail to deepen their understanding.

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3) Questionnaires filled out by students after the course revealed that most students were satisfied with the program because they could deepen their partnership with students of other specialties but were unsatisfied with the program's tight schedule and the inefficiency of discussions.
4) Many instructors felt that the number of students in each group (12 or 13) was too large for effective group discussion.
5) This program helped students understand the importance of communication in medicine but did not encourage students to study for themselves.
Key words: tutorial education, problem-based learning, communication

## 1. 目 的

信州大学では以前から医学部1年次生を対象とした演習科目として「新入生ゼミナール」を実施し，医学科，保健学科の各専攻（看護学，検査技術科学，理学療法学，作業療法学）が個別のプランに基づいて大学生活や各専攻での履修内容の紹介，学習の心構えなどについてオリエンテーションを行ったり，テーマを決めて早期学習を行ったりしてきた．しかし近年はチーム医療の重要性がこれまで以上に認識されており，医学教育の枠組みの中で専攻の異なる学生が一緒に学び，それぞれの専門領域が医療の中で担っている役割を知るための機会を持つことの必要性が高まってきた[1,2]．また，医学教育の中でこれまでの講義中心型教育から問題解決型・自学自習型教育へのシフトが生じており[3]，医学部における新しい教育プログラムの展開が必要になってきた．そこで信州大学医学部では平成16年度から学科間，専攻間の垣根を取り払って新入生をグループ分けし，チュートリアルに準じた形で自学自習やグループ討論を行う，医学部全専攻科合同の「新入生ゼミナール」を開始した．演習の意義と問題点を明らかにするために，実習後に参加学生と教員に対するアンケート調査を行い結果を分析した．

## 2. 対象と方法

信州大学医学部に入学した1年次生全員を対象として5月中旬から7月下旬に，1回90分，全10回の合同演習を行った．本学部における平成17年度の入学者数は医学科95名，保健学科看護学専攻71名，同検査技術科学専攻37名，同理学療法学専攻19名，同作業療法学専攻19名の計241名である．専攻ごとに新入生を20のグループに振り分け，おおむね1グループが医学科4～5名，看護学専攻3～4名，検査技術学専攻2名，理学療法学専攻1名，作業療法学専攻1名から構成されるようにした．チューターは医学科教員が8グループ，保健学科教員が12グループを担当した．チューターに対してはあらかじめ教員向けに作成した「担当教員の手引き」をもとに，実習の進め方や評価法についてのガイダンスを実施した．

平成17年度の日程を表1に示す．第1回は全員が大講義室でオリエンテーションを受け，第2回は専攻ごとの履修内容や卒業後の進路，他専攻の職種との連携などが紹介され，その後グループワークのテーマである医療と接遇に関する約15分間のビデオドラマを視聴した．このビデオは患者がさまざまな医療場面で医療者と接する姿を示すことによって医療者の接遇について考えさせるもので，シナリオ作成，演技，院内での撮影はすべて教員が行った．ドラマの中では以下にシナリオの一部を示すように，医学部学生が院内で患者と出会った場面も取り入れた．

【シーン4—採血室へ行く途中の廊下】
〈田中さん（患者）が廊下でまごつく横を，白衣を着た人たちが忙しそうに通り過ぎていく〉
患者：（白衣を着た学生の2人連れに）すみません，採血室はどこでしょう．
学生1：えっ，あ，おれっスか？
患者：はい．採血室の場所がわからなくて…
学生1：（頭をかきがなら）えーっと，あっちの方だったと思うけど…．検査部のあたりだったかなあ．
学生2：（学生1の白衣の袖を引っ張りながら）