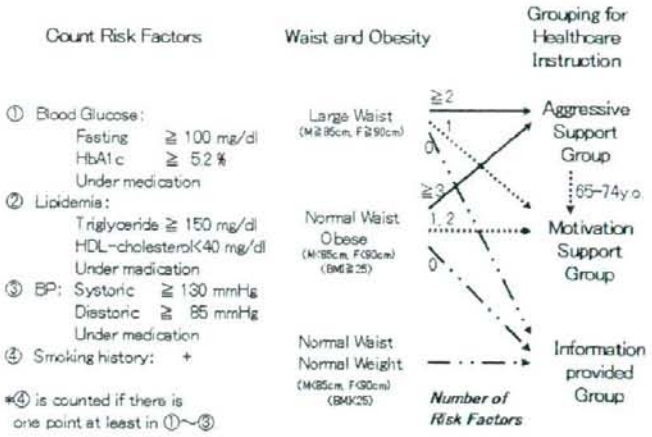


Fig.1 Stratification into risk groups according to the results of physical examination and blood chemistry tests (ref.[5]).

Insurers need to provide healthcare instruction once to individuals assigned to the motivation support group, and repeatedly to individuals assign to the aggressive support group. The information provided group is not given health instruction. A physician, a health nurse, or a registered dietitian should provide the first healthcare instruction each year. Non-face-to-face instruction via telephone or information and communication technology (ICT) system is allowed for additional instruction on the aggressive support group. Insurers do not need to provide healthcare instruction to the person who is under medication of lifestyle disease when he/she is classified into the motivation support group or the aggressive support group.

All data obtained from the PHCS will be digitized in a standard protocol as HL7 CDA and in standard cords as JLAC 10. Insurers will have to maintain records for each insured person as long as he or she remains insured. The records will contain health check-up and instruction data. If the individual changes insurer as he changes occupation, the former insurers will transfer the data to the new insurer so that there is no gap in the record. With these systems in place, it is anticipated that the Japanese government have access to huge amounts of anonymous data that can be used for statistical purposes. Insurers can keep the data without anonymising it because, for example, they have to analyze it together with the receipt data from the medical institutions. Insurers will be able to store data more effectively when the on-line reimbursement project is fully achieved in 2011.

The Japanese government suggests that the insurer pay an additional 10% contribution to medical cost of aged person (age 75 year or over) if it does not achieve the stated goals or be rewarded by a 10% discount if stated goals are achieved from 2013. The Japanese government is asking for a 25% decrease in the number of diabetes and pre-diabetes patients per insurer for example.

Insurers will be allowed to outsource the required tasks to healthcare provider companies. Thus, many tasks will be outsourced to Internet data centers.

The initial action of insurers will be the engagement of a health-care provider company for outsourcing. After registration of the covered citizens, the health-care

provider will begin service. If the providers do not produce adequate outcomes, insurers must pay the penalty. Insurers must take overall responsibility.

Our Research field, "Carna"

A venture company Carna Health Support participated as an outsourcing company for data management with IT system and healthcare instruction. Carna Health Support originally launched to establish a Japanese model of disease management in diabetic field in 2006 by diabetic specialists in Kyushu University and collaborator companies. Thus, Carna has two programs, one is the primary prevention program for PHCS, and another is the secondary/tertiary prevention program for diabetes mellitus.

To motivate clinics and patients to participate in disease management, Carna supports the family doctor system and education for patients.

For clinics, Carna matches doctors and new patients when individuals are affected with a lifestyle disease. Carna also attempts to prevent patient dropout by telephone contact, support patient education and detection of early-stage complications by means of periodic questionnaires, and facilitate medical specialists' cooperation according to the timing described in the critical pathway system.

For patients, Carna promotes guideline medical care described in the critical pathway, report the results of blood tests quickly, and provide 'Carna points' as rewards for the patient's efforts (for instance, regular clinic visits) and for improvement in their diabetic condition (HbA1c). Carna exchanges the points for coupons with which they can obtain certified health-related products such as healthy foods and exercise goods.

(1) Critical pathways for quality control, for appropriate matching of services to individuals, and for adaptation to the political direction in Japan.

Carna developed a region-related, outcome-oriented critical pathway as the core competency in the call center. Carna also standardized workflow in the call center calling 'algorithm'. The critical pathways and the parts of the algorithm are digitized. Carna prepared an education system with structured questionnaires and comprehensive teaching materials, which are closely related to the personalized critical pathway.

Carna had two kinds of outcome-oriented critical pathways by the end of 2006. One is for the primary prevention program (lifestyle improvement program). The other is for the secondary/tertiary prevention program for diabetes mellitus.

Features of the critical pathway for lifestyle improvement program edge are described below;

- Using five kinds of critical pathway matching each stage of Prochaska stage model (pre-contemplation stage, contemplation stage, preparation stage, action stage, maintenance stage) .
- Matching the framework of the PHCS

Features of the critical pathway for diabetes mellitus (secondary/tertiary prevention) that Carna has developed are described below;

- Scheduling of medical services based on clinical guidelines produced by the Japanese Diabetic Society.

- Supporting general care of diabetic outpatients including timely reminders of the need to visit medical specialists such as an ophthalmologist, and a diabetologist.
- Using 'the overlay method' to create an optimal personalized critical pathway for each patient. A personalized critical pathway is created by overlay with a basic sheet for regular examination, and optional sheets matching patient's treatments, the severity of the diabetic complications, and the patient's level of knowledge. Carna can create 2,880 different of critical pathways.
- Modifying continuously as the patient's condition

(2) Personalized communication based-on patient characteristics

Patients' responses to interventions vary because the basic characters of patients vary. For successful intervention, Carna determines the patient's character type during the registration process, and Carna depends on this information to personalize our communication with the patient. This approach may also decrease stress of the call center staff.

(3) Other algorithms and ICT system for efficient and secure data management

Carna developed other algorithms ICT system as shown in Fig.2. Carna used application service provider system for ICT to input participant records.

Carna is using an Internet data center in Fukuoka city, Japan, for database servers. Carna sends data over the Internet via virtual private network from the call center.

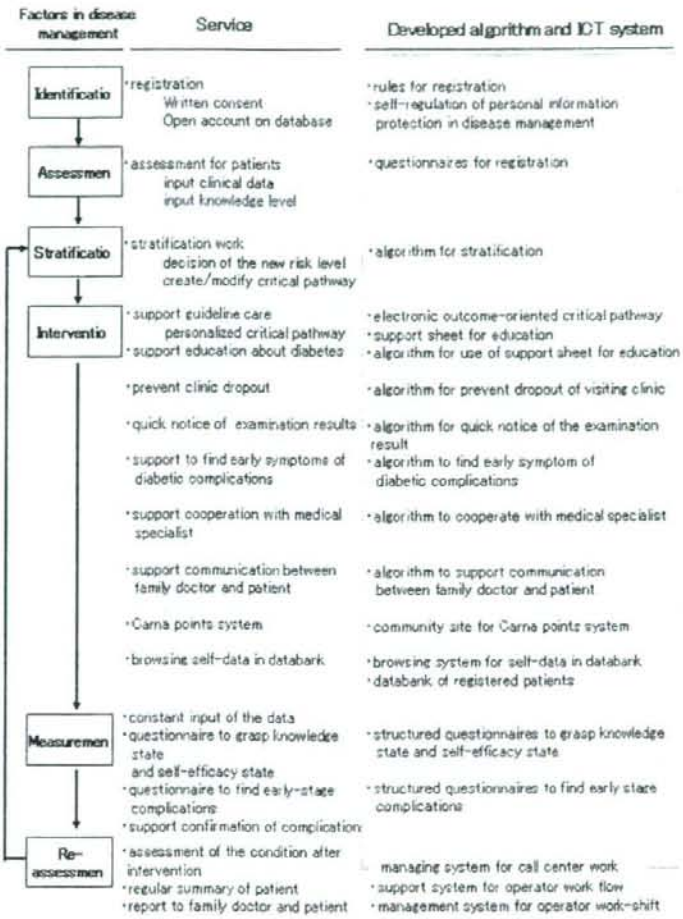


Fig. 2 Disease management services and rules, algorithms, and ICT system in the secondary/tertiary prevention program for diabetes mellitus (ref.[5])

(4) Ethical considerations

Carna quantified the risk of disclosure in terms of information value, threat arising from inadequate ICT security, and areas of vulnerability and showed that the highest risk was posed by databases containing individual patient profiles. Consequently, We believes that we need regulations pertaining to the provision of health information and that we need general classifications for various types of patient information that we deal with in disease management work.

3.2 SOA Based Healthcare using Sensor Network

We aim to develop a SOA based healthcare system of Canra which manages effective PHCS, integrated with sensor networks. Using sensor network with vital sensors, the activities and lifestyles of patients/citizens can collected in an easy and accurate manner, and therefore effective healthcare can be possible.

However, since the entire system will be highly complex system, the following issues have to be considered.

Scalability

Since the medical check system is to be applied to massive populations in long term, the system has to handle huge amount of data. Distributed architecture which can process massive data will be needed. Especially, maintenance cost in an wide area distribution should be seriously considered.

Heterogeneity

The system should handle various kinds of data, such as manually input data, sequential motion sensor data, and periodical vital sensor data. Along with this, sensors and networking devices will also be heterogeneous to meet with the varieties of required data and reliability.

Reliability

Because of the variety of data and of the requirement for long battery life of mobile sensor devices, there should appear trade-offs between accuracy of data and energy consumption. For example, we can analyze the movement of an patient more accurately and more in real time if we could obtain frequent motion data from an accelerometer, but it results in severe battery life. Optimal balance of these parameters should be discovered for reliability of data.

Human Friendliness

Since the system is to be used in the daily lives of patients, it should be highly user-friendly as much as stress free to patients. It has the following two aspects:

- Human interfaces such as web interfaces should be easy to use, and easy to be embedded to the patients' lifestyles, so as in the case of blog systems.
- Vital sensor devices should be non-intrusive, small as much as possible, and even free in the way of attaching to the body. For example, a heart rate sensor attached to the finger keeps the patient away from desk work.

Security and Privacy Management

The data handled in the system are sometimes highly privacy-sensitive ones. Therefore, complete security and adequate personal data access control are the necessary.

Flexibility

This is the most important feature. Although we addressed the above requirement for the system, we still do not know how much we should decide the qualitative or quantitative parameters or implementations from so many design options.

It means that we fundamentally need many experiences and trials, that we should adopt the style of rapid development based on the feedbacks from the trials. Here, the reason why SOA, which realizes highly modularized composition of service functions, is crucial in this healthcare domain.

4 Experience

In this section, the experience aimed for effective medical check systems are described. In the experience, sensor network was introduced for automatically monitoring the activity of patients, and for advising the patients adequately. Moreover, the obtained data from the sensors as well as manually recorded data can be used for medical knowledge discovery which is unknown so far.

4.1 Design

For simplicity, we classify the users of the system into two roles: patients, and data analyst. *Patients* are the users who resulted in the need for continuous care by specific medical check. *Data analysts* are the users who analyze the data from the sensors along with the manually recorded data, and correspond to physician, health adviser in the specific medical check system, and medical researcher in actual situation.

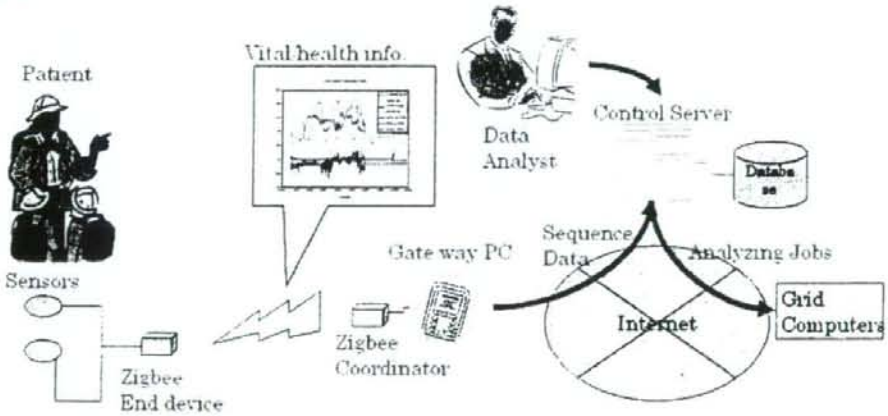


Fig.3 System and Network Architecture

Fig. 3 is the system and network architecture of the system. The system consists of sensors, zigbee[8] end devices, zigbee coordinator, gateway PC, control server, database, and grid computers. The use cases of the system are described in the following.

Patient

Patients have sensor end devices in their lives. End devices attached with sensors acquire vital data of the patients periodically, and send them to zigbee coordinator through routers.

Routers, coordinators, and gateways are placed in offices and homes, and receive data from the end devices, and send to the control server. Gateway PCs also accept manual inputs from the patients.

Data Analyst

Data analysts do data analysis, or data mining using the data gathered to the control server.

The control server stores the data from gateway PCs to the database systems, and throws analysis/mining jobs by data analysts to grid computers, with the data, and receives the answer.

4.2 Consequence

Based on the architecture introduced above, we tried a first-step experience, where basic design options, such as communication protocols, communication throughput, human friendliness of sensor devices, sensor measurement methods, are discovered with reasonably small amount of population in a single place.

The trial was done in a building which has a hospital and a fitness club at once. 3 patients participated at one time, and repeated 3 times for independent groups, which means 9 patients in total.

The trial was scheduled as the following:

1st day: medical check (Fig. 4(a))

In the first day, the patients took full-fledged medical check, including blood, urinalysis, ECG, X-ray, body consumption, BMI, blood pressure, and CPX(cardiopulmonary exercise).

Especially, CPX (Fig.4(a)) has an important factor. In CPX, an adequate heart rate can be calculated from variety of measurements such as the rate of O2 and CO2 in breath during an exercise. This value of heart rate can be used in the exercises in the following days.

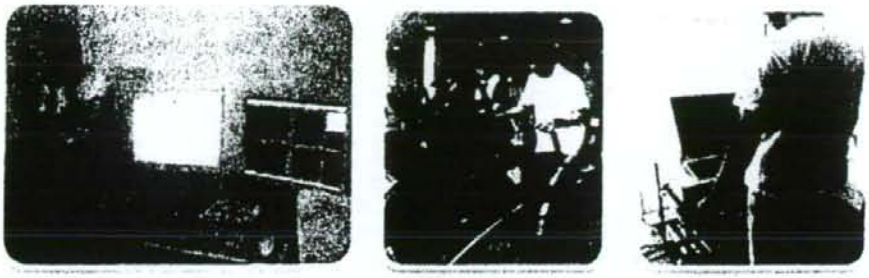
2nd~7th day: exercise and dietary program (Fig.4 (b))

From the next day, the patients take fitness exercises, including body stretch, aerobic exercise, and muscle training, for about 2 hours.

Besides, the patients are managed dietary program. 2 of the meals in a day are designated by a dietitian, and diet soup and diet frozen food are sent to the home of the patients. And what they ate in the rest of the day are interviewed and recorded by the dietitian. To be accurate, this is done from the 1st day.

8th day: measurement of the effects (Fig.4(c))

After the days of exercises and dietary program, the effect of the exercises and diets are evaluated by measuring the change of blood factors, urinalysis, body composition, BMI, and blood pressure.



(a)1st day (b)2nd~7th day (c) 8th day

Fig. 4 Scene of trial

Sensor and zigbee devices

For this trial, we used the following sensor devices

- 2D / 3D accelerometers
- Temperature, humidity, and light sensors
- Heart rate sensors (non-zigbee)
- Heart rate sensors (non-wireless)

Fig. shows one type of the sensor zigbee devices, which has 2D accelerometers, temperature, humidity, and light sensors, and gateway PC.

Fig. 5 Sensor Zigbee devices and gateway PC

Obtained Data

Through the trial, obtained data are the following:

- Medical check of the 1st day, such as blood tests, body/athletic abilities, body compositions, urinalysis, and thoracic pictures,
- CPX data of the 1st day(
- Lifestyle related inqury to the patients
- Record of excercises from 2nd to 7th days, such as weight of before/after, blood pressure of before/after, and, time, number, expected calorie of each exercise item.
- Sensor data of exercise hours(
- Calorie intake during the dietary program, and,
- The change of blood test, BMI, body composition in the 8th day.

After all, detailed data for analysis or data mining could be successfully obtained through the trial.

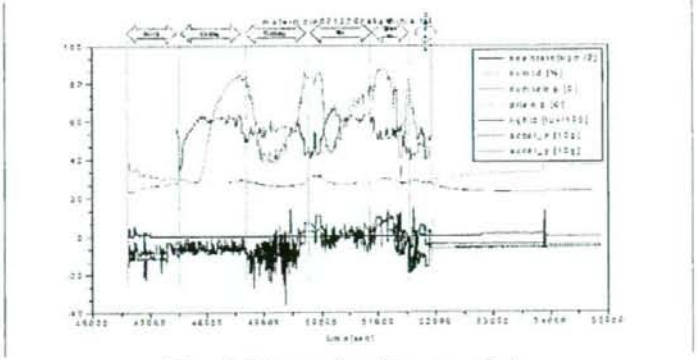


Fig. 6 Example of sensor data

5 Conclusion

Here, we discuss the aspects of SOA in the sensor based medical domain we experienced.

First of all, SOA is often discussed in the context of web systems, which means online and homogeneous system. However, we tried ubiquitous environment where network is not always online, and many kinds of small devices which sometimes has no programmability to developers. It addresses many future challenges to SOA environments.

For scalability, we acknowledged the ease of maintenance of zigbee protocol. Multi-hop communication can extend the communication area, and easy handshake protocol reduces the time and maintenance cost of reconnect.

For heterogeneity, the only device types we could adapt to was one which has open source OS , and on site functionality of updating software. This kind of flexibility must be required although it might affect the device cost and power consumption.

For reliability, we could reduce the sampling frequency of accelerometer to several Hz while keeping the accuracy of activity recognition, which leaded to the longer battery life.

For human friendliness, not only intrusive sensors which we did not use, but also types of sensors which had to be fixed on specific places of a body, such as a heart rate sensor on the chest or on the finger, and an accelerometer which was designated to be fixed on the back, was hated by patients. On the other hands, sensors which are designated to be placed in any place on the body such as a pocket, were easier to use, while they reported practically accurate data, such as an accelerometer, temperature, and humidity sensors.

Security and privacy management, and flexibility on the server side are the future challenges to be discussed to fit SOA.

Acknowledgement

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Korean Medical Association became aware of this issue and has been trying to look for a medical doctor to take charge of online counseling on Jisik-iN of NAVER.

A growing number of doctors and healthcare administrators believe that online communication between physicians and patients is no longer an "if" but a "when" [7]. There is already a growing demand for Internet-based health services including physician-patient communication such as Internet health consultation among Korean. Asynchronous medical consultations will likely complement some face-to-face meetings [8, 9].

In this context, more doctors have to be aware of the need for online medical counseling and more appropriate and accurate medical information should be provided by medical doctors on online medical counseling.

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Disease Prevention/Management Model and Nationwide Standardized Health Check-up Program in Japan

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Abstract— In 2008, the Japanese government started a nationwide disease prevention program for lifestyle disease combined health check-up, risk-stratification and health counseling. The object number of the health check-up program is 56 millions and the object number of health counseling is 14 millions at a maximal. Additionally, we may find - 4 millions of diabetic patient who do not visit clinics. Many of stakeholders will participate to support the program, thus, Japanese government strongly standardized the methods of health check-up and health counseling. The document format (HL7 CDA-R2) and code (JLAC10) in the program are also standardized. We conducted a verification study of the health counseling program as a disease management/prevention program provider in 2007. We found that the stratification logic and the health counseling way are appropriate in the viewpoint of cost-effectiveness. Although this national program still remains problems, we believe the risk management for diabetes mellitus will be achieved by this new program and establishment of disease management program for clinical diabetes in Japan.

Keywords—Health Check-up, Metabolic Syndrome, Diabetes Mellitus, HL7 CDA R2

I. INTRODUCTION

The public survey in 2006 showed that there were 10.5 millions of pre-diabetic and 8.2 millions of diabetic patients in 127 millions of Japanese population. A half of the patients do not visit clinic. This trend is worldwide and yielding a lot of patients with severe complications such as atherosclerosis (stroke and ischemic heart disease) and chronic renal failure with hemodialysis.

The Japanese government started a new lifestyle disease prevention program 'Tokutei Kenshin' for all

Japanese citizens aged 40 – 74 years (56 millions people) in April 2008[1, 2]. This program is aiming nationwide standardization of health check-up and health counseling ways. It also promotes standardization and interoperability of health data using HL7 CDA-R2 and standardized code JLAC10 to use them on IT system. Here we report the outcomes of a verification study of the health counseling program in 2007.

II. Natioanlwide Health Check-up And Counseling Program

A. Particular health check-up program "Tokutei Kenshin"[2]

All Japanese citizens are covered by public medical insurance. This new health check-up is the duty of insurers. The annual health check-up includes a questionnaire, a physical examination, and a blood chemistry tests.

After the health check-up, insurers have to stratify participants into three risk groups by the view of visceral fat accumulation.

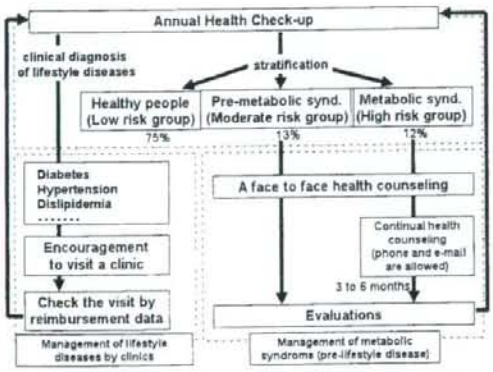

Fig. 1 Outline of the new nationwide health check-up system in Japan. The system started from April 2008. Health counseling is not provided to participants who are taking medicines.

Insurers need to provide health counseling to moderate and high risk groups, and repeatedly to high risk group for 3 months at least, maximally 6months.

If the results of physical or blood examination are in pathologic ranges, the insurer have to determine individually if the insurer only provides health counseling or encourages the participants to visit a clinic. The pathologic ranges are decided in this program.

1) Blood glucose
   Fasting > 126 mg/dl or
   HbA1c > 6.1%
2) Blood lipids
   Triglyceride > 300 mg/dl
   or
   HDL-cholesterol < 35 mg/dl
3) Blood pressure
   Systoric > 140 mmHg or
   Diastoric > 90 mg/dl
4) LDL-cholesterol > 140 mg/dl

B. HL7 CDA R2 and JLAC10 in the system

All data obtained from the health check-up and counseling should be digitized in a standard document format derived from HL7 CDA-R2[3]. Two document types are defined from one message model. One is health check-up reporting document, which has laboratory test results section and interview results section. Another is health consultation reporting document, which has consultation plan section, consultation results section, and claim information section for reimbursement.

All of the laboratory data are coded in JLAC 10, which is standard code system for laboratory tests in Japan, and can be converted into LOINC. Data of physical examination including blood pressure and waist are coded into JLAC-10 compatible style code.

Insurers will have to maintain records for each insured person as long as he or she remains insured. If the individual changes insurer as he changes occupation, the former insurers will transfer the data to the new insurer. Insurers are allowed to outsource the required tasks to health check-up and health counseling provider companies. Thus, many stakeholders will participate in this program and make a huge transaction of data. That is why the government strictly regulates the standardized data document protocol and code. There will be no gap in the record if they deal the data appropriately. With these systems in place, it is anticipated that the Japanese government have access to huge amounts of anonymous data that can be used for statistical purposes. Insurers can keep the data without anonymising it because, for example, they have to analyze it together with the reimbursement data from the medical institutions. Insurers will be able to store data more effectively when the on-line reimbursement project which is another nationwide project, is fully achieved in 2011.

The Japanese government suggests that the insurer pay an additional 10% contribution to medical cost of aged person (age 75 year or over) if it does not achieve the stated goals or be rewarded by a 10% discount if stated goals are achieved from 2013. If the providers do not produce adequate outcomes, insurers must pay this financial penalty. Insurers must take overall responsibility.

III. Verification Study

We conducted a verification study of the new health check-up and counseling system with cooperation of 4 company's insurers in 2007 (Table 1). We used pared-t test for statistical evaluation.

49 % of participants were in low risk, but 10 % and 28 % were in moderate and high risk groups. 15 % of participants were taking medicine.

Major parts of participants (63.8%) have some of data in pathologic ranges. Participants who have data in pathological range of diabetes mellitus are 18 out of 257.

Table 1 Stratification results of health check-up. 21 (8.2%) out of 257 were female. (L; low risk group, M; moderate risk group, H; high risk group, Med; medicated group)

Company insurers	(n)	Stratification L M H Med (n (%))	Life style dis.(n) (Diabetic(n))	Age at health check (y-o)	Weight before intervention (kg)	BMI before intervention	Waist before intervention (cm)
A Co.	157	81 16 41 19 (52 10 26 12)	93 (9)	47.21 ±4.76	68.02 ±9.25	23.64 ±2.78	84.89 ±7.42
B Co.	22	10 5 5 2 (46 23 23 9)	15 (0)	45.32 ±8.10	71.67 ±8.55	24.82 ±2.51	87.17 ±6.36
C Co.	49	15 3 17 14 (31 6 35 29)	40 (7)	51.12 ±5.08	70.21 ±8.96	24.00 ±2.72	86.51 ±5.60
D Co.	29	17 1 8 3 (57 3 27 10)	16 (2)	50.62 ±9.40	64.28 ±13.71	23.36 ±3.26	83.82 ±8.69
Total	257	123 25 71 38 (49 10 28 15)	164 (18)	48.18 ±6.12	68.33 ±9.87	23.78 ±2.81	85.28 ±7.20

To evaluate the stratification logic and the health counseling program, we provided "continual health counseling to all participants in the study for 6months.

Table 2. The loss of weight by health counseling.

Groups	n	Loss of weight±SE (kg)	p value
All	**190**	**0.88 ± 0.24**	**0.0004**
Low risk	90	0.11 ± 0.26	0.6600
Moderate risk	22	0.41 ± 0.64	0.5303
High risk	**50**	**2.50 ± 0.63**	**0.0002**
taking medicine	28	0.80 ± 0.56	0.1662
No pathologic data in any items	70	-0.05 ± 0.31	0.8686
With pathologic data	120	1.42 ± 0.33	<.0001

Table 3 The loss of waist by health counseling.

Groups	n	Loss of waist±SE (cm)	p value
All	**159**	**1.35 ± 0.39**	**0.0006**
Low risk	76	0.84 ± 0.62	0.1763
Moderate risk	17	1.09 ± 0.67	0.1260
High risk	**42**	**2.39 ± 0.68**	**0.0012**
taking medicine	24	1.35 ± 1.00	0.1918
No pathologic data in any items	55	0.74 ± 0.64	0.2505
With pathologic data	**104**	**1.68 ± 0.48**	**0.0007**

Table 2, 3 show the outcomes of health counseling. 67 out of 257 participants could not be communicated and be considered to drop out during health counseling. We could not get waist data from 31 participants after health counseling.

In all participants who did not drop out, weight and waist are improved significantly. However, better improvements have been achieved in high risk group (metabolic syndrome), with decreases of 2.50 kg in weight and 2.39 cm in waist.

IV. Discussion And Conclusion

From the results of verification study, we concluded that the stratification logic and health counseling program which Japanese government provided us are appropriate for company's insurers. However, the delay of fixation of program work flow, insurers are still confusing in October 2008. IT systems are not working well in many insurers because of inadequate preparation. Additionally, the shortage of advertisement to citizens makes a low utilization rate of the program in the half way of the fiscal year of 2008.

Major parts of participants (63.8%) have some of data in pathologic ranges in the verification study (Table 1). These pathologic ranges seem to be too strict if examination is only once, thus, the health check-up data

of many people might touch the ranges by mere chance. However, the "encouragement to clinic" should be most important task in the program. As mention in "Introduction", a half of diabetic patients do not visit clinics. Medical effort never reaches them if they do not visit medical institutes. The nationwide health check-up program may resolve this problem. As shown in Fig. 2, the program may find maximum 4 millions of diabetic patients, who do not visit clinics. Huge amounts of HL7CDA data will circulate between insurers and medical institutions.

Risk management of diabetic patients of all Japanese citizens will be expected in Japan if the particular health check-up program works. Next step must be establishment of effective disease management program for diabetes mellitus in medical field.

V. Acknowlegments

We sincerely appreciate Kyuden Infocom Co., Kyushu Electric Power Co., and Tokyo Marine Nichido Co., for their support of this study.

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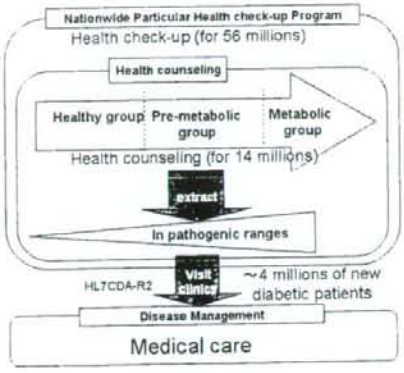

Fig. 2 Relation of the particular health check up program and medical field. Maximal numbers are shown in the figure. Focusing in diabetes mellitus, maximum 4 millions of diabetic patients who ignore the disease, are targets of encouragement to visit clinics.

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Nationwide Standardized Health Check-up/Counseling Program in Japan

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Abstract— In 2008, the Japanese government started a nationwide disease prevention program for lifestyle disease combined health check-up, stratification by risk, and health counseling for risk group. The object number of the health check-up program is 56 millions and the object number of health counseling is 14 millions at a maximal. Additionally, we may find - 4 millions of diabetic patient who do not visit clinics, besides other 4 millions are visiting clinics now. Japanese government strongly standardized not only the items and methods of health check-up and counseling, but also the document format (HL7 CDA-R2) and code (JLAC10) in the program to enable many stakeholders to participate to support the program. Thus, accumulated data, which each insurer will keep, should be a main source of electronic health record (EHR) in Japan. We and Carna Health Support LLC conducted a verification study of the health counseling program as a disease management/prevention program provider in 2007. We found that the stratification logic and the health counseling program are appropriate in the viewpoint of cost-effectiveness. Although this national program still remains problems, we expect the risk management for lifestyle diseases will be achieved by this new disease prevention program and establishment of disease management program for clinical lifestyle diseases in Japan.

Keywords—Disease Management, Metabolic Syndrome, Lifestyle Diseases, Diabetes Mellitus, HL7 CDA R2

I. Introduction

The public survey in 2006 showed that there were 10.5 millions of pre-diabetic and 8.2 millions of diabetic patients in 127 millions of Japanese population. A half of the patients do not visit clinic. This trend is worldwide and yielding a lot of patients with severe complications such as atherosclerosis (stroke and ischemic heart disease) and chronic renal failure with hemodialysis.

The Japanese government started a new lifestyle disease prevention program 'Tokutei Kenshin' for all Japanese citizens aged 40 – 74 years (56 millions people) in April 2008[1, 2]. This program is aiming nationwide standardization of health check-up and health counseling ways. It also promotes standardization and interoperability of health data using HL7 CDA-R2 and standardized code JLAC10 to use them on IT system. Here we report the outline of the program and the outcomes of a verification study of the health counseling program we conducted in 2007.

II. Nationwide health check-up and counseling program

II-1. Particular health check-up program "Tokutei Kenshin"[2]

All Japanese citizens are covered by public medical insurance. This new health check-up/counseling program is the duty of insurers. The annual health check-up includes a questionnaire, a physical examination, and a blood chemistry tests.

After the health check-up, insurers have to stratify participants into three risk groups by the view of visceral fat accumulation.

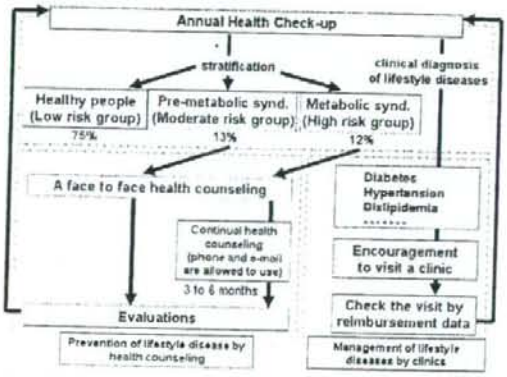

Fig. 1 Outline of the new nationwide health check-up system in Japan. The system started from April 2008. Health counseling is not provided to participants who are taking medicines.

Insurers need to provide health counseling to moderate and high risk groups, and repeatedly to high risk group for 3 months at least, maximally 6months.

If the results of physical or blood examination are in pathologic ranges, the insurer have to determine individually if the insurer only provides health counseling or encourages the participants to visit a clinic. The pathologic ranges are decided in this program.

1) Blood glucose

Fasting	>	126 mg/dl	or
HbA1c	>	6.1%	

2) Blood lipids

Triglyceride	>	300 mg/dl	or
HDL-cholesterol	<	35 mg/dl	

3) Blood pressure

Systolic	>	140 mmHg	or
Diastolic	>	90 mg/dl	
4) LDL-cholesterol	>	140 mg/dl	

II-2. HL7 CDA R2 and JLAC10 in the system

All data obtained from the health check-up and counseling should be digitized in a standard document format derived from HL7 CDA-R2[3]. Two document types are defined from one message model. One is health check-up reporting document, which has laboratory test results section and interview results section. Another is health consultation reporting document, which has consultation plan section, consultation results section, and claim information section for reimbursement.

All of the laboratory data are coded in JLAC 10, which is standard code system for laboratory tests in Japan, and can be converted into LOINC. Data of physical examination including blood pressure and waist are coded into JLAC-10 compatible style code.

Insurers will have to maintain records for each insured person as long as he or she remains insured. If the individual changes insurer as he changes occupation, the former insurers will transfer the data to the new insurer. Insurers are allowed to outsource the required tasks to health check-up and health counseling provider companies. Thus, many stakeholders will participate in this program and make a huge transaction of data. That is why the government strictly regulates the standardized data document protocol and code. There will be no gap in the record if they deal the data appropriately. With these systems in place, it is anticipated that the Japanese government have access to huge amounts of anonymous data that can be used for statistical purposes. Insurers can keep the data without anonymising it because, for example, they have to analyze it together with the reimbursement data from the medical institutions. Insurers will be able to store data more effectively when the on-line reimbursement project which is another nationwide project, is fully achieved in 2011.

The Japanese government suggests that the insurer pay an additional 10% contribution to medical cost of aged person (age 75 year or over) if it does not achieve the stated goals or be rewarded by a 10% discount if stated goals are achieved from 2013. If the providers do not produce adequate outcomes, insurers must pay this financial penalty. Insurers must take overall responsibility.

III. Verification Study

We conducted a verification study of the new health check-up and counseling system with cooperation of 4 company's insurers in 2007 (Table 1). We used pared-t test for statistical evaluation.

49 % of participants were in low risk, but 10 % and 28 % were in moderate and high risk groups. 15 % of participants were taking medicine.

Major parts of participants (63.8%) have some of data in pathologic ranges. Participants who have data in pathological range of diabetes mellitus are 18 out of 257.

Table 1 Stratification results of health check-up[4]. 21 (8.2%) out of 257 were female. (L; low risk group, M; moderate risk group, H; high risk group, Med; medicated group)

Company	(n)	Stratification L M H Med (n(%))	(Diabetic(n))			
A Co.	157	81 16 41 19 (52 10 26 12)	53 (9)	47.21 ±4.76	60.02 ±9.25	23.64 ±2.78	81.89 ±7.42
B Co.	22	10 5 5 2 (46 23 23 9)	15 (0)	45.32 ±8.10	71.67 ±8.55	24.82 ±2.51	87.17 ±6.36
C Co.	49	15 3 17 14 (31 6 35 29)	40 (7)	51.12 ±5.08	70.21 ±8.06	24.00 ±2.72	85.51 ±5.60
D Co.	29	17 1 8 3 (57 3 27 10)	16 (2)	50.62 ±9.40	64.28 ±13.71	23.36 ±3.26	83.82 ±8.69
Total	257	123 25 71 38 (49 10 28 15)	164 (18)	48.18 ±6.12	68.33 ±9.87	23.78 ±2.81	85.28 ±7.20

To evaluate the stratification logic and the health counseling program, we provided "continual health counseling to all participants in the study for 6months.

Table 2, 3 show the outcomes of health counseling. 67 out of 257 participants could not be communicated and be considered to drop out during health counseling. We could not get waist data from 31 participants after health counseling.

In all participants who did not drop out, weight and waist are improved significantly. However, better improvements have been achieved in high risk group (metabolic syndrome), with decreases of 2.50 kg in weight and 2.39 cm in waist.

Table 2. The loss of weight by health counseling[4].

Groups	n	Loss of weight ± SE (kg)	p value
All	190	0.88 ± 0.24	0.0004
Low risk	90	0.11 ± 0.26	0.6600
Moderate risk	22	0.41 ± 0.64	0.5303
High risk	50	2.50 ± 0.63	0.0002
taking medicine	28	0.80 ± 0.56	0.1662
No pathologic data in any items	70	-0.05 ± 0.31	0.8686
With pathologic data	120	1.42 ± 0.33	<.0001

Table 3 The loss of waist by health counseling[4].

Groups	n	Loss of waist±SE (cm)	p value
All	159	1.35 ± 0.39	0.0006
Low risk	76	0.84 ± 0.62	0.1763
Moderate risk	17	1.09 ± 0.67	0.1260
High risk	42	2.39 ± 0.68	0.0012
taking medicine	24	1.35 ± 1.00	0.1918
No pathologic data in any items	55	0.74 ± 0.64	0.2505
With pathologic data	104	1.68 ± 0.48	0.0007

IV. Discussion and Conclusion

From the results of verification study, we concluded that the stratification logic and health counseling program which Japanese government provided us are appropriate for company's insurers. However, the delay of fixation of program work flow, insurers are still confusing in October 2008. IT systems are not working well in many insurers because of inadequate preparation. Additionally, the shortage of advertisement to citizens makes a low utilization rate of the program in the half way of the fiscal year of 2008.

To increase the cost effectiveness of the health counseling program, we are now trying to use sensor devices. These devices provide us objective and real time physical data of the participants. These decrease time which is needed to know the change of lifestyle, and increase the accuracy of the data and safety by avoiding risky exercise and diet[5].

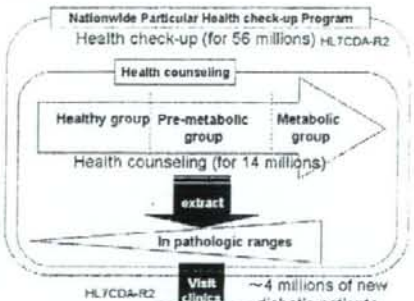

Fig. 2 Relation of the particular health check up program and medical field. Maximal numbers are shown in the figure. Focusing in diabetes mellitus, maximum 4 millions of diabetic patients who ignore the disease, are targets of encouragement to visit clinics.

Major parts of participants (63.8%) have some of data in pathologic ranges in the verification study (Table 1). These pathologic ranges seem to be too strict if examination is only once, thus, the health check-up data of many people might touch the ranges by mere chance. However, the system of "encouragement to clinic" should be most important task in the program. As mention in "Introduction", a half of diabetic patients do not visit clinics. Medical effort never reaches them if they do not visit medical institutes. The nationwide health check-up program may resolve this problem. As shown in Fig. 2, the program may find maximum 4 millions of diabetic patients, who do not visit clinics. Huge amounts of HL7CDA data will be circulated between insurers and medical institutions.

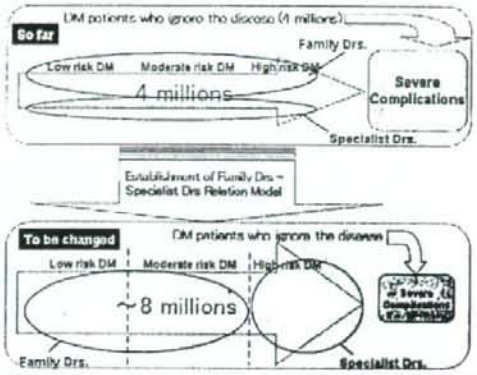

Fig. 3 To reduce severe complications of diabetes, we need establish a effective "family doctors – specialist doctors relation model. Specialist doctors should be focused on the high risk group to manage.

Risk management of diabetic patients of all Japanese citizens will be expected in Japan if the particular health check-up program works. Next step must be establishment of effective disease management program for diabetes mellitus in medical field to manage high risk group (Fig. 3).

V. Acknowledgments

We sincerely appreciate Kyuden Infocom Co., Kyushu Electric Power Co., and Tokyo Marine Nichido Co., for their support of this study.

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The Lack of the C-Terminal Domain of Adipose Triglyceride Lipase Causes Neutral Lipid Storage Disease through Impaired Interactions with Lipid Droplets

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Context: The molecular mechanisms by which triglycerides in lipid droplets (LDs) are synthesized, stored, and degraded need to be elucidated.

Objective: The objectives were to report siblings with neutral lipid storage disease with myopathy (NLSDM) with a novel mutation of adipose triglyceride lipase (ATGL) and determine whether the C-terminal part of ATGL containing the hydrophobic region plays a role in the interaction with LDs.

Design and Patients: Skin fibroblasts and peripheral blood leukocytes were obtained from NLSDM patients. *In vitro* experiments were performed with fibroblasts and COS7 cells.

Main Outcome Measures: Transfection studies were used to assess the effects of various recombinant ATGL proteins on lipase activities and lipid contents. Fluorescence microscopy were used for determination of intracellular distribution of ATGL proteins.

Results: The direct sequence of ATGL cDNA reveals that a patient is a homozygote for the 4-bp deletion, leading to a premature stop codon and causes the lack of the C terminus of the protein including the hydrophobic domain. Overexpressed control ATGL in NLSDM fibroblasts was found around the rims of LDs and caused significantly reduced cellular lipid accumulation. In contrast, NLSDM ATGL was homogeneously located in the cytoplasm despite the presence of LDs and had almost no effect on LD degradation despite its similar lipase activity. A series of C-terminal truncated ATGLs without the intact hydrophobic domain failed to localize around and degrade LDs.

Conclusions: These findings indicate that the domain including the hydrophobic region of ATGL was essential for association with LDs. (***J Clin Endocrinol Metab* 93: 2877–2884, 2008**)

Lipid droplets (LDs) are the main energy reservoir for triglycerides in eukaryotic cells. The molecular mechanisms by which triglycerides in LDs are synthesized, stored, and degraded need to be elucidated to overcome health problems such as obesity, metabolic syndrome, and type 2 diabetes mellitus that are now issues in developed countries. Neutral lipid storage diseases (NLSDs) are characterized by the presence of intracellular triglyceride deposition in most tissues, including leukocytes (Jordans' anomaly) (1), bone marrow, skeletal muscles, heart, and the liver. Chanarin-Dorfman syndrome (CDS; MIM 27630) (2, 3) is an autosomal recessive type of NLSD with ichthyosis. Lefevre *et al.* (4) reported that the mutation of comparative gene identification 58 (CGI-58) (5) was a cause of CDS (4). However,

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Abbreviations: ATGL, adipose triglyceride lipase; CDS, Chanarin-Dorfman syndrome; CGI-58, comparative gene identification 58; GFP, green fluorescence protein; LD, lipid droplet; NLSD, neutral lipid storage disease; NLSDM, NLSD with myopathy.

some NLSD patients have also been reported without ichthyosis or mutation in the CGI-58 gene (6).

Hormone sensitive lipase has been thought to be the main lipase in LDs. However, the fact that hormone sensitive lipase-deficient mice show a nonobese phenotype and accumulation of diglycerides means that there are several other triglyceride lipases (7, 8). In 2004 three groups independently reported a new lipase; named as adipose triglyceride lipase (ATGL) (9), desnutrin (10), and calcium-independent phospholipase A2ξ (11), which catalyzes the initial step in triglyceride hydrolysis.

Lass *et al.* (12) demonstrated that the triglyceride hydrolase activity of ATGL was activated by CGI-58 up to 20-fold. Smirnova *et al.* (13) showed that ATGL was located around LDs with a tail-interacting protein of 47 kDa, an LD-associated protein, and in nonadipocyte HeLa cells. Its overexpression caused a marked decrease in lipid droplet size, whereas short interfering RNA-induced knockdown resulted in an increase in size. They also showed an ATGL mutant lacking S47 in the phospholipase domain that reduces lipase activity existed around LDs but failed to decrease LD size. In addition, Haememerle *et al.* (14) reported that ATGL-depleted mice showed triglyceride deposition in most tissues. Their data suggested that ATGL is another causative gene for NLSDs. Recently Fischer *et al.* (15) reported a NLSD subgroup characterized by mild myopathy, an absence of ichthyosis, and mutations in both the alleles of ATGL [NLSD with myopathy (NLSDM)]. Three of these mutations were predicted to lead to a truncated ATGL protein with a patatin-like phospholipase domain and without the C-terminal domain including hydrophobic amino acid-rich region (residues 309–391). They showed that normal whole-cell lipase activity but low lipid droplet-associated lipase activity in NLSDM fibroblasts. These results suggest that the mutant ATGL they used for experiments keeps lipase activity but impairs the interaction with LDs. However, the detailed role of the C-terminal region of ATGL remains to be elucidated.

Here we report two NLSDM siblings that have a novel homozygous ATGL mutation together with clinical investigations and show that the C-terminal part of ATGL containing the hydrophobic region has an important role in localizing around LDs.

Patients and Methods

Sequencing of ATGL cDNA of the patient

Both patients signed informed consent forms for this study, which was approved by the Ethics Review Committee of Kyushu University. Total RNA samples were prepared from the patient's fibroblasts and white blood cells from a control individual using Isogen (Nippon Gene, Tokyo, Japan). Oligo dT primer-primed cDNA was made from total RNA with a Superscript first-strand synthesis system for RT-PCR (Invitrogen Life Technologies, Carlsbad, CA). These cDNAs were used as templates for PCR. The primers used were based on the human patatin-like phospholipase domain-containing protein 2 nucleotide sequence (GenBank accession no. NM_020376) and were as follows: 5′-AGCGAGCGAGCGGCGAGCAG-3′ and 5′-GGCGTCTCAGGCAGGGTTCC-3′. PCRs were carried out in a 50-μl volume containing 5% dimethylsulfoxide using KOD-Plus-version 2 (Toyobo, Osaka, Japan): the initial denaturation step was performed at 94 C for 2 min, followed by 35 cycles of 10 sec at 98 C, 30 sec at 64 C, 1.5 min at 68 C, and a 5-min terminal elongation step. The nucleotide sequences of the PCR products were determined using an ABI PRISM 377 DNA sequencer (Applied Biosystems, Tokyo, Japan). For subcloning to expression plasmids, the sequences containing the complete open reading frame of human ATGL were amplified by PCR. The primers were designed to create endonuclease cleavage sites (underlined): human ATGL forward 5′-CGGGATCCTTTCCCCGCGAGAAGACGTG-3′, and human ATGL reverse 5′-CCCTCGAGCTCACAGCCCCAGGGCCCC-3′. The PCR fragments were digested with *Bam*HI or *Xho*I and subcloned into the eukaryotic expression vector pcDNA4/HisMax C (Invitrogen). A pcDNA4/HisMax vector with β-galactosidase (LacZ) was provided by the manufacturer. After confirming the sequences, plasmids were prepared for transfection using a QIAfilter plasmid maxikit (QIAGEN, Tokyo, Japan). A series of truncated control ATGLs were generated using a Kilo-sequence deletion kit (Takara BIO, Tokyo, Japan) and subcloned into the green fluorescence protein (GFP)-expression vector, pEGFP-C1 (CLONTECH, Palo Alto, CA).

Cell culture and transfection with expression vectors

Fibroblasts obtained from the patient's tissue and Simian virus-40-transformed African green monkey kidney cell lines (COS7) were cultured with DMEM (400 mg/dl glucose; Sigma, St. Louis, MO) containing 10% fetal bovine serum, 100 U/ml penicillin, 100 μg/ml streptomycin, and 2 mM [SCAP]l-glutamine. In some experiments, cells were incubated overnight with 300 μM oleate complexed to BSA to increase the synthesis and storage of triglycerides in LDs. The patient's fibroblasts and COS7 cells were transfected with various expression vectors using Lipofectamine LTX and Plus Reagent (Invitrogen). After transfection for 24–48 h, cells were used for experiments.

Fluorescence microscopy

For determination of GFP-ATGL fluorescence, cells were cultured on 35-mm coverslip-bottomed dishes (Magtek, Ashland, MA) and transfected with the appropriate plasmids. Fluorescence imaging of GFP-ATGL was assessed by confocal laser-scanning microscopy (TCS-SP system; Leica Microsystems, Heidelberg, Germany). Cells were imaged for GFP by excitation with the 488-nm line from an argon laser and emission viewed through a 496-to 550-nm band-pass filter. To correlate the localization of GFP-ATGL with the intracellular structure, cells were viewed with fluorescence and Oil red O staining images.

For Oil red O staining (16), cells were washed twice with PBS and then fixed by soaking in 10% formalin for 10 min at room temperature. After being washed with PBS and incubated with 60% isopropanol for 1 min, cells were stained for 20 min at room temperature in freshly diluted Oil red O (Sigma) solution (six parts of Oil red O stock and four parts of H_2O; Oil red O stock solution is 0.3% Oil red O in isopropanol). The staining solution was removed and the cells washed with 60% isopropanol and then twice with PBS. Next, nuclei were stained with hematoxylin (Muto Pure Chemicals, Tokyo, Japan). Stained cells were examined under a light microscope (Nikon, Tokyo, Japan). Fluorescence imaging of GFP-ATGL and Oil red O was assessed by confocal laser-scanning microscopy. Imaging of Oil red O was provided by excitation with the 568-nm line, and the emission was viewed through a 580- to 660-nm band-pass filter.

The measurement of intracellular lipid contents

For the determination of triglyceride contents in the patient's fibroblasts, cells were washed with PBS and total lipids were extracted with 3:2 hexan-isopropanol, brought to dryness, and solubilized in 0.1% Triton X-100. Triglyceride was measured using triglyceride E test (Wako, Osaka, Japan). Protein concentrations were determined with BCA protein assay reagent kit (Pierce, Rockford, IL) using BSA as standard.