BRIEF COMMUNICATION

One Hundred Case Studies of Asia-Pacific Telemedicine Using a Digital Video Transport System over a Research and Education Network

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Abstract

Although the use of video in telemedicine is most helpful, the transmission of high-quality moving images is difficult in conventional systems due to the limitation of network bandwidth and the quality of service. We have established a new system via the academic broadband network that can preserve the original quality and assure smooth movement of the image. Here we report on 100 case studies and discuss the lessons we have learned. Kyushu University Hospital in Fukuoka, Japan, was linked to 53 medical institutions and meeting venues in 13 countries and regions over the Asia-Pacific Advanced Network, an international research and education consortium. The digital video transport system (DVTS), free software that transforms digital video signals directly into Internet Protocol, was installed on a personal computer (PC) with a network bandwidth of 30 Mbps per channel. Between February 2003 and June 2007, 100 telecommunication sessions were held, 94 of which were international and 6 domestic. Furthermore, 47 involved real-time demonstrations and 53 interactive teleconferences using video or PC presentations. Multiple stations were connected in 37 events, and the number of connected stations in total reached 269. The time delay was restricted to 0.3–1.0 seconds between the stations. Participants provided feedback via questionnaires, and with respect to image quality, 509 (68.3%) participants reported "very good," 206 (27.7%) reported "good," 19 (2.6%) reported "poor," and 11 (1.5%) reported "very poor." DVTS is both economical, with a minimal initial investment, and simple to set up, and this is the first time that this advanced system has been used so widely in the Asia-Pacific region. Because the high-speed academic network for research and education is available worldwide, we believe our cutting-edge technology will facilitate medical standardization beyond geographic borders in the world.

Key words: *telemedicine, digital video transport system, research and education network, surgery, endoscopy*

Introduction

The use of moving images is of great assistance in education. This is especially true in medicine because it is much easier to understand both routine procedures and new techniques by actually seeing them, rather than by only reading medical textbooks with static images or scientific papers. Despite its huge potential, conventional telemedicine remains popular mainly for transmitting still pictures such as pathological and radiological images, as it has failed to achieve practical satisfactory quality in transmitting moving images.[1] An Integrated Services Digital Network (ISDN) or commercially available Internet degrades the quality to a

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greater or lesser extent, due to the limitation of the transmittable information volume and the necessity of its compression.[2-5]

The digital video transport system (DVTS) together with the research and education network (REN) have completely changed this situation. DVTS is software that can convert digital video signals directly into Internet Protocol (IP) without any analog conversion.[6] Owing to its much larger bandwidth (30 Mbps/line) than conventional methods such as ISDN (0.128 Mbps/line), it can transmit moving images with the original quality suitable for medical purposes.[7] Meanwhile, the REN, which was established by government and is now available in many countries worldwide, can be used for academic purposes to secure a stable and large enough bandwidth for DVTS.[8] Although this newly developed system has advantages of both high quality and low cost, it is not well known in the medical community and only a limited number of papers have been published.[9-15]

Here we report on 100 case studies in the Asia-Pacific region using these two key technologies.

Materials and Methods

SYSTEM

We used DVTS, which employs differentiated data transmission, for sending full-resolution moving images to the remote stations. The details were reported previously.[9] In brief, the system uses freely downloadable software (http://www.sfc.wide.ad.jp/DVTS/) installed in a personal computer (PC). A digital video (DV) camera or the video output from medical devices was connected via an IEEE 1394 interface to a PC with access to broadband Internet. The necessary bandwidth was 30 Mbps per channel and audio was transmitted simultaneously with the image. To protect patient privacy, we used security program, C4S-VPN (Focus Systems Co., Japan) or IPsec (AR550S, AlliedTelesis K.K., Japan) during live demonstrations. The ethics committee of Kyushu University Faculty of Medicine approved the project, and informed consent was obtained from each patient prior to the event.

To connect multiple stations with DVTS, we used the QualImage/Quatre system (Information Services International-Dentsu, Ltd., Tokyo, Japan), which was originally developed to distribute uncompressed digital images to four different sites without any analog conversion. The server was located at the Computing and Communications Center in Kyushu University, and the DVTS signals were sent from four different places. The signals were digitally merged onto one screen and sent back to each station. The current version has been upgraded to control up to 16 sites. We measured the actual time latency between the screens of connected stations as described previously.[13]

RESEARCH AND EDUCATION NETWORK

Kyushu University Hospital in Fukuoka, Japan, was first linked to Korea in February 2003 via the high-speed broadband Internet of the REN. The network was subsequently extended to other countries in the Asia-Pacific region, including China, Taiwan, Thailand, Singapore, the Philippines, Vietnam, Indonesia, India, Malaysia, Australia, and the United States, giving a total of 13 countries/regions.

The Kyushu University campus network was connected to two domestic 10-Gbps RENs, the Japan Gigabit Network (JGN2), and the Science Information Network 3 (SuperSINET3). International lines were provided by the Asia-Pacific Advanced Network (APAN), which is an international consortium of network organizations working for research and development of communications and information technology, and also by the Trans-Eurasia Information Network after January 2006. The domestic RENs in the other countries include the Korea Advanced Research Network in Korea, the China Education and Research Network (CERNET) and the China Science and Technology network in China, the Hong Kong Academic and Research Network in Hong Kong, the Taiwan Advanced Research and Education Network and the Academic Sinica in Taiwan, the Thai Research and Education Network in Thailand, the Singapore Advanced Research and Education Network in Singapore, the Philippine Research Education and Government Information Network in the Philippines, the Vietnam Research and Education Network in Vietnam, the Indonesian Higher Education Network, Education and Research Network in India, Malaysia Research and Education Network, the Australian Research and Education Network in Australia, and Internet2 in the United States.

EVALUATION OF QUALITY OF IMAGES AND INTEREST IN THIS PROJECT

Questionnaires were used to evaluate both the quality of the moving images and the interest in joining our activities. Possible responses to questions were "very good," "good," "poor," and "very poor," for the former case, and "very much," "much," "little," and "very little," for the latter.

Results

Between February 2003 and June 2007, 100 teleconferences were held for medical purposes using DVTS over the REN. Ninety-four were international connections with a total of 53 connected stations, and 6 were for domestic use within Japan. Universities or hospitals were connected in 73 events with a permanent network, while convention centers or hotels were connected in 27 events with temporary lines. There are 15 connected sites in Japan, 11 in Korea, 4 in China, 5 in Taiwan, 3 in Thailand, 1 in Singapore, 2 in the Philippines, 2 in Vietnam, 2 in Indonesia, 1 in India,

Table 1. List of Activities and Connected Countries/Regions

	COUNTRY OR REGION													
	JP	KR	CN	TW	TH	SG	PH	VN	ID	IN	MY	AU	US	TOTAL
Live demonstrations														
Surgery	31	27	11	4	1	5	3	0	0	2	1	1	0	86
Endoscopy	15	5	1	1	2			1				2		27
Hematology	5	3			1									9
Medical informatics	1	1												2
Others	1		1											2
Subtotal	53	36	13	5	4	5	3	1	0	2	1	3	0	126
Teleconferences with video or computer presentations														
Surgery	15	14	2	3	1	1						1		37
Endoscopy	9	6	3	2	1									21
Transplantation	8	5	3	2								1		19
Hepatobiliary pancreas	6	7		1										14
Hematology	2	1	1		2									6
Medical informatics	3			1										4
Nursing and healthcare	13	5	1		3	1	1	1	2			1	2	30
Others	6	3		1		1							1	12
Subtotal	62	41	10	10	7	3	1	1	2	0	0	3	3	143
Total number of connected stations	115	77	23	15	11	8	4	2	2	2	1	6	3	269

JP, Japan; KR, Korea; CN, China; TW, Taiwan; TH, Thailand; SG, Singapore; PH, the Philippines; VN, Vietnam; ID, Indonesia; IN, India; MY, Malaysia; AU, Australia; US, The United States.

1 in Malaysia, 4 in Australia, and 2 in the United States. The time delay was restricted to 0.3–1.0 second between connected sites.

Real-time demonstrations were performed in 47 events, while 53 events consisted of interactive teleconferences using recorded video or PC presentations. Pier-to-pier connections were made in 63 events, whereas multiple stations were connected in the remaining 37 events; three stations in 15 events, four stations in 20 events, and more than five in 2 events. The number of connected stations reached 269 in total. The contents of the teleconferences are listed in *Table 1* according to country or region. Surgeries, which covered general surgery, neurosurgery, urology, and robotic surgery, were most popular both in the live demonstrations and teleconferences (*Fig. 1*). The second favorite was endoscopy in live demonstrations, and healthcare in teleconferences (*Fig. 2*). Japan and Korea were the most active countries, followed by China, Taiwan, and Thailand.

When the series of case studies was divided into five groups, each with 20 events according to time, the activity rapidly expanded from Korea–Japan to other Asia-Pacific regions as shown in *Figure 3*, with the majority

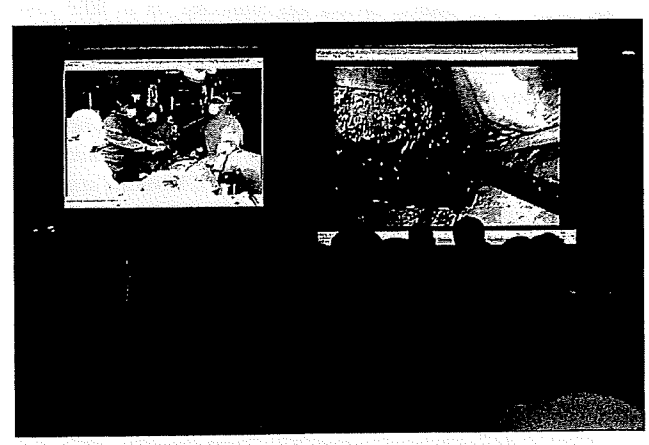

Fig. 1. Live demonstration of surgery. A view of the operating room on the left screen and of the surgery on the right at the congress venue in Seoul, Korea, using two channels of digital video transport system.

:onnected outside Korea–Japan in the most recent two groups. Similarly, nultistation settings increased steadily in number, reaching two thirds vith three-site connections or more in the most recent 20 events (*Fig. 4*).

With respect to image quality, 745 participants responded to the uestionnaires, with 509 (68.3%) reporting "very good," 206 (27.7%) good," 19 (2.6%) "poor," and 11 (1.5%) "very poor," as shown in *Figure 5*. Similarly, with respect to their interest in this project, 436 (65.7%) of 665 reported "very much," 173 (26.1%) reported "much," 16 (2.4%) reported "little," and 40 (6.0%) reported "very little."

ig. 2. Four-station teleconference of endoscopy, connecting Kyushu University Hospital (top left), Sapporo meeting venue (top ight) in Japan, Shangnai Jiaotong University in China (bottom eft), and National Cancer Center in Korea (bottom right), using QuallImage/Quatre.

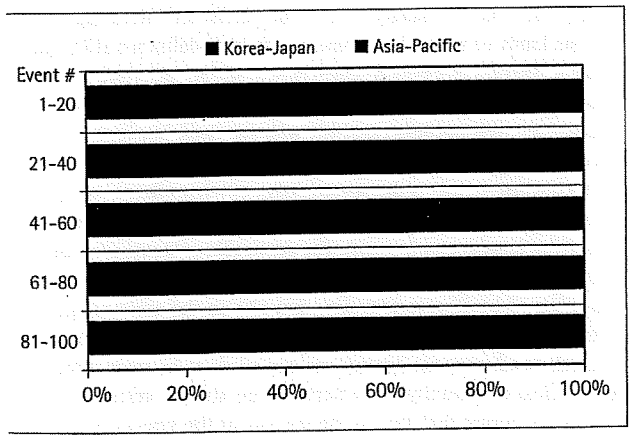

Fig. 3. The ratio of connections between Korea–Japan and Asia-Pacific for each group of 20 events.

Discussion

DVTS, whose basic technology is internationally qualified as DV over IP by the Internet Engineering Task Force of Internet Society, has many advantages over conventional systems such as ISDN or narrow band telemedicine where heavy compression is mandatory to make transmission possible within the limits of the transmittable information volume. Because DVTS consumes as much as 30 Mbps

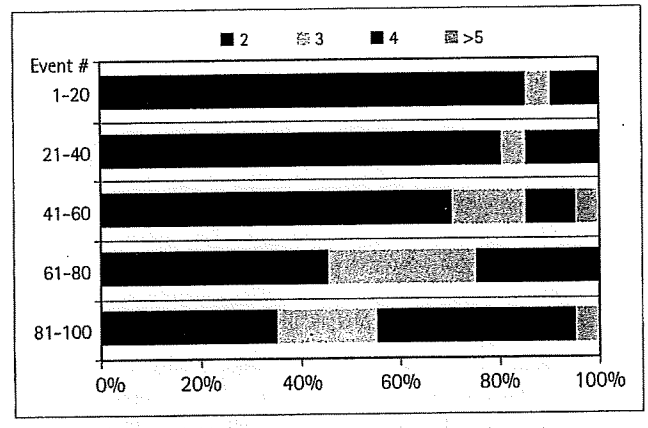

Fig. 4. The number of connected stations for each group of 20 events.

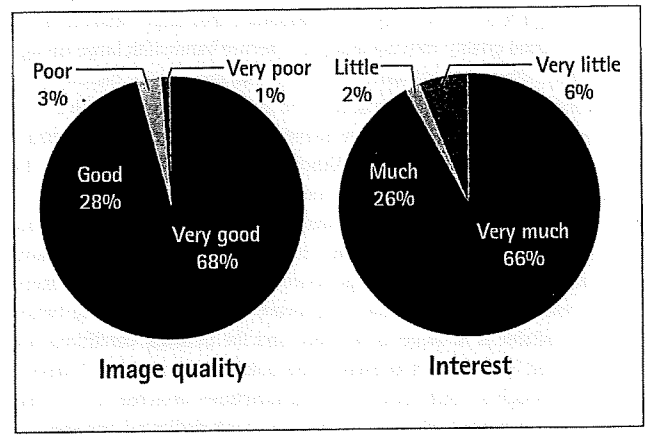

Fig. 5. Analysis of the questionnaires about image quality (left) and interest in the activity (right).

per channel, which is over 200 times larger than ISDN, compression can be minimal, thus maintaining the original quality of the moving images over the transmission.[7] It is quite reasonable that low bandwidth connections showed slow and sluggish movements of the remote video image, as reported by Broderick et al.[16] and Rabenstein et al.[17] regarding the effects of various transmission bandwidths on image quality. Demartines et al.[18] also pointed out the degraded image of a surgery from the Picturetel videoconferencing system (Picturetel Corp., Danvers, MA) using the H.323 compression algorithm.

After our events started between Japan and Korea in 2003, many medical doctors in neighboring countries/regions were attracted and this led to rapid expansion in the Asia-Pacific area, due to the system's benefits of simplicity and economy, yet powerful performance.[13] It is quite understandable that surgery was the most popular content, because watching surgical streaming with precise anatomy at a remote site or learning decision-making processes during surgery is a very convincing and convenient educational tool for surgeons.[5,19–21] As shown by the increase in multistation connections, more and more medical institutions wanted to join these teleconferences, which included both clear moving images and interactive discussions. Although a subjective assessment of the image quality of motion pictures must adhere to standard methods and additional study is necessary to further analyze the negative answers given for both image quality and interest of the contents, the brief evaluations by the participants verified the good image quality of our system and the attractiveness thereof.[22] Because of the complexity of the compression algorithms inevitable in conventional systems, skipping this time-consuming process resulted in minimal time delay between connected institutions over a wide area of the Asia-Pacific region.

Although it is theoretically well understood that large bandwidth can transmit good quality moving images, to secure bandwidth large enough for DVTS with stable conditions is a different story. If the bandwidth is insufficient or unstable, this will ruin the image quality even with DVTS. Therefore, the REN is another key element in our study and is necessary to take full advantage of DVTS. Although Internet is similarly used, the REN is completely different from the one widely used in daily life.[8] It is a government-funded network dedicated to research and education, and is already connected to major universities and medical institutions in many countries. Although this network is widely used by engineers, most health providers are not even aware of its existence. The bandwidth available is as large as 10 Gbps and the network conditions are finely tuned by engineers at each access point 24 hours a day, 7 days a week. Although a small packet loss was sometimes detected at receiving sites, the loss is minimal owing to the use of this dedicated and specialized network. The biggest advantage is that it is free for end users in already connected institutions in exchange for limiting the contents thereof not to be used for commercial or profit-making purposes. The REN is not only available in developed countries, but is also rapidly expanding into many developing countries other than those with which we shared our project. In Japan, for example, there is a national REN called SuperSINET3 connecting all national universities. Internet2 is the national REN in the United States connecting 200 major universities, while CERNET in China has connected as many as 1,000 universities. APAN is an international REN connecting these domestic RENs mainly in the Asia-Pacific region, and GEANT2 is a European REN connecting 34 countries. Although Damore et al.[23] successfully used the Internet2 broadband network, they merely adopted a conventional compression protocol and thus failed to take full advantage thereof.

The proposed telemedical system using DVTS and the REN is more useful for learning skills or techniques through live demonstrations and recorded videos rather than just for exchanging medical knowledge. Compared with video-on-demand streaming systems, bidirectional real-time discussion provides audiences with truly necessary information.[24] It was not difficult to run this activity at normal times in the Asia-Oceania region where the time differences are only a few hours. As far as our experience is concerned, it has been well accepted by medical personnel, and more useful in international settings with different medical standards. To make this activity even more attractive, however, the further development of technologies is awaited. QualImage/Quatre is currently the only equipment we can use to establish multistation teleconferences, but it is only compatible with the NTSC format used in Japan, Korea, the United States, etc. To involve phrase alternating line (PAL) countries such as China and many others in Southeast Asia, we had to use converters or to supply them with NTSC cameras. In addition, demands for even better quality than the DV quality (720 × 480 pixels) are increasing because various kinds of medical equipment with high-definition (HD) quality (1920 × 1080 dpi) are now commercially available, including for surgery and endoscopy. We have already reported a successful transmission of live surgery with uncompressed HD with 1.6 Gbps, but further study is necessary to supply the huge bandwidth and to reduce the cost.[25]

In conclusion, this is the largest series of telemedicine using DVTS over the REN and the system is very attractive in terms of good quality moving images and low cost. The applicable contents are unlimited and we are exploring future potential uses of this system not only for education of healthcare providers, but also in the areas of specialist referral services and patient consultations. The REN is open to any research or educational institutions and needs to be more utilized by the medical community. New partners are always welcome, but we should not forget that key to the success of the system is the close cooperation between medical and engineering staff.

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isclosure Statement

No competing financial interests exist.

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Confirmation of Multiple Risk Loci and Genetic Impacts by a Genome-Wide Association Study of Type 2 Diabetes in the Japanese Population

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OBJECTIVE—To identify novel type 2 diabetes gene variants and confirm previously identified ones, a three-staged genome-wide association study was performed in the Japanese population.

RESEARCH DESIGN AND METHODS—In the stage 1 scan, we genotyped 519 case and 503 control subjects with 482,625 single nucleotide polymorphism (SNP) markers; in the stage 2 panel comprising 1,110 case subjects and 1,014 control subjects, we assessed 1,456 SNPs ($P < 0.0025$, stage 1); additionally to direct genotyping, 964 healthy control subjects formed the in silico control panel. Along with genome-wide exploration, we aimed to replicate the disease association of 17 SNPs from 16 candidate loci previously identified in Europeans. The associated and/or replicated loci (23 SNPs; $P < 7 \times 10^{-5}$ for genome-wide exploration and $P < 0.05$ for replication) were examined in the stage 3 panel comprising 4,000 case subjects and 12,569 population-based samples, from which 4,889 nondiabetic control subjects were preselected. The 12,569 subjects were used for overall risk assessment in the general population.

RESULTS—Four loci—1 novel with suggestive evidence (*PEPD* on 19q13, $P = 1.4 \times 10^{-5}$) and three previously reported—were identified; the association of *CDKAL1*, *CDKN2A/CDKN2B*, and *KCNQ1* were confirmed ($P < 10^{-19}$). Moreover, significant associations were replicated in five other candidate loci: *TCF7L2*, *IGF2BP2*, *SLC30A8*, *HHEX*, and *KCNJ11*. There was substantial overlap of type 2 diabetes susceptibility genes between the two populations, whereas effect size and explained variance tended to be higher in the Japanese population.

CONCLUSIONS—The strength of association was more prominent in the Japanese population than in Europeans for more than half of the confirmed type 2 diabetes loci. ***Diabetes* 58: 1690–1699, 2009**

The predisposition to and the course of type 2 diabetes vary according to ethnic group (1–3). In Japan, the incidence of type 2 diabetes has increased recently and is now comparable to that of other countries; this is supposedly attributable to the gradual spread of Western habits, such as consuming a high-fat diet, and the lower insulin secretory capacity of Japanese subjects (4,5). Recent technological developments have allowed the successful identification of gene regions involved in the development of type 2 diabetes in genome-wide association (GWA) studies (6–17). Several susceptibility gene loci identified by GWA studies to date have been used to obtain reproducible evidence of disease association in different populations of European descent and Asians, but not necessarily in African Americans (18–24). A number of GWA studies on type 2 diabetes have been conducted on populations of European descent (6–12). Two GWA scans in the Japanese population simultaneously reported the discovery of type 2 diabetes susceptibility gene (*KCNQ1*) variants in non-European populations; this result was also obtained in Scandinavian samples (25,26). Thus far, the replicated associations for a limited number of candidate genes have broadly indicated the tendency of interethnic similarity. Even though the common (or cosmopolitan) effect of type 2 diabetes risk variants is known, the extent to which the causation of this disease differs or overlaps between populations remains unknown. Here, besides comparing the genetic associations between European-descent and Japanese populations, we aimed to identify new genetic variants using a three-staged GWA study design.

RESEARCH DESIGN AND METHODS

Detailed characteristics of the subjects enrolled in each stage are described in the supplementary information and in supplementary Table S1, which is available in an online appendix at http://diabetes.diabetesjournals.org/cgi/content/full//db08-1494/DC1. Briefly, patients and unaffected control subjects analyzed in stages 1 and 2 were enrolled depending on whether they met certain uniform criteria. Type 2 diabetes was diagnosed according to 1999 World Health Organization criteria. All stage 1 and 2 control subjects (≥55

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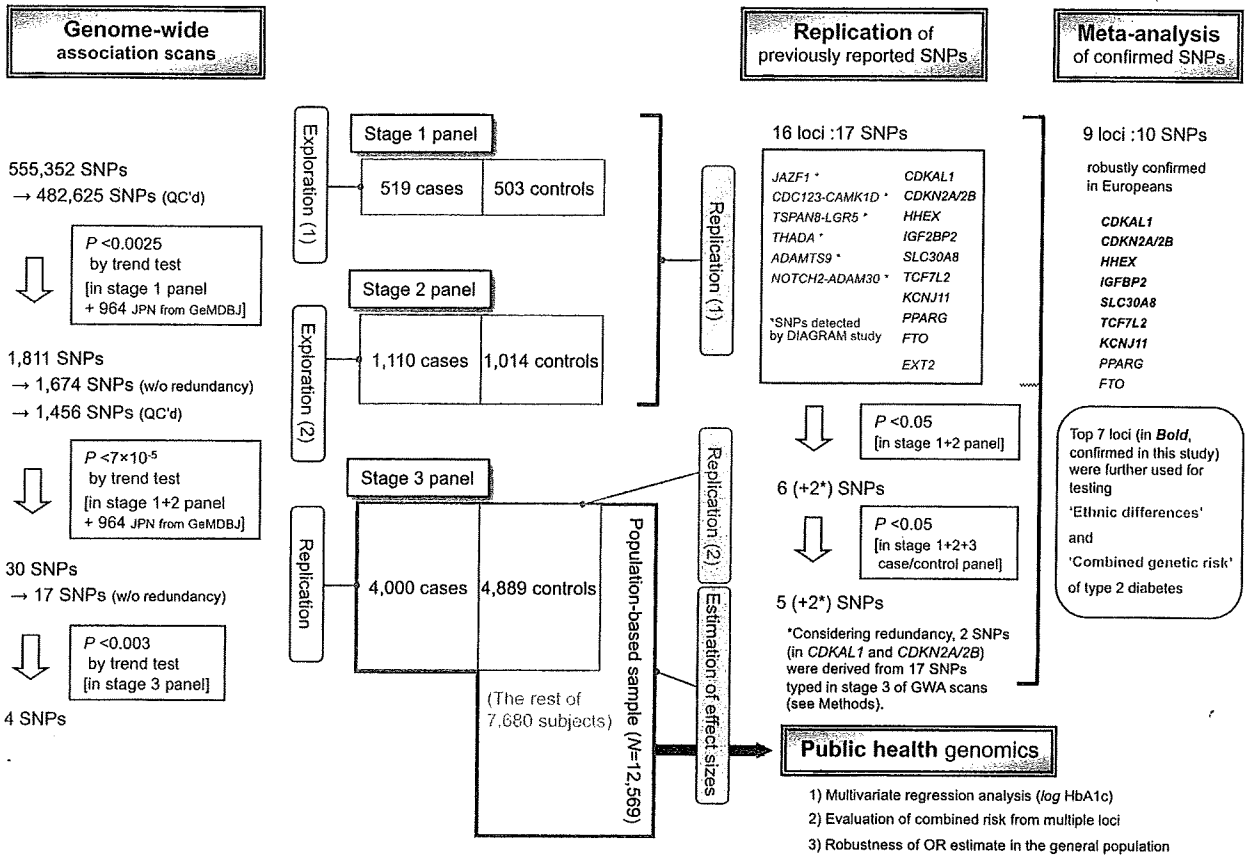

FIG. 1. Flow chart summarizing the multistage design and study aims. (A high-quality digital representation of this figure is available in the online issue.)

years of age at examination) had normal glucose tolerance. The stage 3 samples comprised 4,000 type 2 diabetes case subjects derived from the Biobank Japan project (http://biobankjp.org/) (27) and 12,569 subjects randomly selected from residents aged 50–74 years in the general population. The 12,569 subjects were used as a population panel; this panel contained 4,889 nondiabetic subjects who met the following conditions: age ≥55 years, A1C ≤5.0%, no previous and/or current treatment for diabetes, and absence of renal failure (serum creatinine <3.0 mg/dl). In stage 3, these 4,889 control subjects were used in a replication study wherein their genotypes were compared with those of 4,000 patients. In addition to the samples genotyped here, to boost the power of the GWA scan, we incorporated genotype frequencies in the general Japanese population (n = 964) derived from the Genome Medicine Database of Japan (GeMDBJ; http://gemdbj.nibio.go.jp), which was used as an in silico control panel. A flowchart summarizing the multistage design and study aims is shown in Fig. 1.

Stage 1 genome-wide scan and quality control. Genotyping was performed with the Infinium HumanHap550 BeadArray (Illumina), which interrogated 555,352 SNPs (supplementary information). The average call rate was 96.9% for the case and control subjects. Data cleaning and analysis were performed using PLINK software (28). Samples with a genotype call rate of <90% were excluded, as were outliers with respect to the number of heterozygous SNPs, duplicates or relatives of another sample, or ethnic outliers. We excluded SNPs for the following reasons: *1*) GenTrain genotype quality score <0.53, *2*) genotype call rate <0.95, *3*) genotype call rate <0.99 and minor allele frequency (MAF) <0.05, *4*) significant ($P < 10^{-6}$) deviation from the Hardy-Weinberg equilibrium in the control subjects, or *5*) MAF <0.001 (supplementary Table S2); the remaining 482,625 SNPs were analyzed.

Analysis of stage 1 genotype data. Ethnicity was verified for 1,022 samples (519 case and 503 control subjects) in the stage 1 panel with reference to data from HapMap populations (29) (see supplementary information). Type 2 diabetes association was tested with the Cochran-Armitage trend test in the stage 1 panel and an additional panel of 964 random control subjects. We pooled the genotype counts for combining multiple panels. To detect and correct population stratification and unnoticed differences in data processing between facilities, the test statistic was adjusted using Eigenstrat software (30) and the genomic-control method (31). The significance level for the first-stage scan was set to $P < 0.0025$; significant SNPs were additionally chosen using Fisher's χ^2 test ($P < 0.0025$) to combine the association results with the P value at the same locus in our previous affected sib-pair scan (32). A total of 1,811 SNPs surpassed the stage 1 threshold, and we removed redundant SNPs that were in mutual strong linkage disequilibrium ($r^2 > 0.9$) before proceeding to stage 2 (see supplementary information and supplementary Fig. S1 and Table S2 for detailed analysis).

Stage 2 genotyping and analysis. Stage 2 genotyping was performed with iPLEX (Sequenom) and GoldenGate (Illumina) assays. Quality control was conducted as described in stage 1, and 1,456 SNPs were successfully genotyped. We calculated P values with the trend test by combining 1,517 nondiabetic control subjects with 964 random control subjects similar to stage 1. The significance level for the second-stage scan was set to $P < 7 \times 10^{-5}$ in the comparison between 1,629 case subjects and 2,481 control subjects (i.e., the stage 1 + 2 panels and the 964 random control subjects). A total of 30 SNPs representing 17 unique loci remained significant.

Replication of previously reported SNPs. Along with genome-wide exploration, type 2 diabetes association was tested in the stage 1 and 2 panels using the HumanHap550 BeadArray, iPLEX assay, or TaqMan method (Applied Biosystems) for 17 SNPs from 16 candidate loci previously identified by GWA studies in populations of European descent (6–17). These included *IGF2BP2* (rs4402960), *PPARG* (rs1801282), *CDKAL1* (rs7754840 and rs7756992), *SLC30A8* (rs13266634), *CDKN2A/CDKN2B* (rs10811661), *HHEX* (rs1111875), *TCF7L2* (rs7903146), *EXT2* (rs3740878), *KCNJ11* (rs5219), *FTO* (rs8050136), *JAZF1* (rs864745), *CDC123-CAMK1D* (rs12779790), *TSPAN8-LGR5* (rs7961581), *THADA* (rs7578597), *ADAMTS9* (rs4607103), and *NOTCH2-ADAM30* (rs10923931). The significant SNPs (trend test, $P < 0.05$) were further analyzed in the stage 3 panel with the TaqMan method. Despite finding significant association for *CDKAL1* and *CDKN2A/CDKN2B* in the stage 1 and 2 panels, we proceeded with rs4712523 instead of rs7754840 and rs7756992 (*CDKAL1*) and with rs2383208 instead of rs10811661 (*CDKN2A/CDKN2B*) in the GWA scans from stage 1 to stage 3; this decision was made considering the

strong linkage disequilibrium between the SNPs in each of the corresponding loci.

Stage 3 genotyping and analysis. The stage 3 design involved the replication of association and the estimation of effect sizes in the GWA scan and/or replication study of previously reported SNPs. For an association to be considered significant in the case-control comparison (4,000 case vs. 4,889 nondiabetic control subjects), it had to involve the same risk allele as that in the previous stages, and it was accordingly assessed with a one-tailed test. For each SNP locus confirmed in stage 3, the association of additional independent SNPs or haplotypes in the locus was also tested (supplementary information). Moreover, to assess the risk of diabetes and pre-diabetes in the general population from the combination of SNPs robustly confirmed both in populations of European descent and in our panel, multiple regression analysis was performed with the logarithm of A1C (log A1C) as a response variable (supplementary information), using the entire 12,569-subject population-based sample.

Meta-analysis of other type 2 diabetes case-control studies in the Japanese population. In addition, for SNPs with robustly confirmed association in populations of European descent, we performed a meta-analysis by combining our stage 1 + 2 (rs1801282, rs7756992, and rs8050136) or stage 1 + 2 + 3 results (the remaining seven SNPs shown in supplementary Figure S2) with those of previous Japanese studies conducted by three other groups (19–21,33–36). According to Woolf's test (37), the heterogeneity among the studies in the Japanese population was insignificant ($P > 0.05$), with the exception of *PPARG* rs1801282 ($P = 0.0012$), for which the observed heterogeneity is supposedly attributable to low allele frequency. Thus, we pooled genotype counts across the studies to form a combined dataset for the Japanese population, and we estimated the effect sizes of individual loci. We used the rmeta package for R software (http://www.r-project.org) for the analysis.

Moreover, to compare the explained variance between the Japanese population and populations of European descent, we calculated the coefficient of determination R^2 for the loci confirmed in our replication study. Here, R^2 is the square of the correlation between the genotypes of an SNP coded by the number of risk alleles (0, 1, and 2) and the disease status (0 and 1) (supplementary information).

RESULTS

GWA scans. Of 482,625 SNPs that passed quality control in stage 1, genotypes were obtained for an average of 99.8% markers for each subject. The subjects were enrolled from regions of Japan with no strong population stratification (38), and although some variance inflation partly attributable to the subtle subpopulation structure was apparent, such confounding influences could be sufficiently removed using Eigenstrat (30) and genomic-control adjustment (31). A total of 1,456 markers were assessed in the stage 2 panel (Fig. 1 and supplementary Fig. S1 and Table S2).

After the second-stage scan, 30 SNPs representing 17 unique loci attained the arbitrarily defined statistical significance ($P < 7 \times 10^{-5}$) (supplementary Table S3). We used one SNP each from these 17 loci in the third-stage scan. Of 17 SNPs, 4 reached the significance threshold of $P < 0.003$ (= 0.05/17) with Bonferroni correction.

The current GWA study showed strong and highly consistent evidence for disease association of SNPs from *CDKAL1*, *CDKN2A/CDKN2B*, and *KCNQ1* (Fig. 2 and Table 1 and supplementary Tables S4 and S5). Although these three loci had already been reported in previous GWA studies (8,11,25,26), here they were identified as part of our genome-wide exploration. *CDKAL1* is among the best-replicated susceptibility loci. Significant association has also been detected in a region on chromosome 9p, near *CDKN2A/CDKN2B*. Moreover, strong association signals were observed in the intron of *KCNQ1* on chromosome 11p15.5, which is in agreement with the results of two previous GWA scans in the Japanese population (25,26).

Stage 2 genotyping provided evidence suggestive of a new association on chromosome 19q13. Several SNPs located in the vicinity of the *PEPD* (peptidase D) gene showed the tendency of replicated association in stages 1 and 2 (supplementary Table S3). Significant association was further replicated in a relatively large case-control study on the stage 3 panel (rs10425678, $P = 0.002$), but it did not attain genome-wide significance (i.e., $P = 1.4 \times 10^{-5}$ for all stages and $P = 2.1 \times 10^{-6}$ when the number of control subjects was increased by adding 964 random control subjects) (supplementary Table S4). Given the modest strength of association ($R^2 = 0.0017$, see below) assumed for this locus, the association still needs to be established.

Replication of previously reported SNPs. Of 16 candidate loci tested for replication in the Japanese population, 7 were found to be associated with type 2 diabetes (Table 1). However, no significant association was observed for SNPs from the remaining nine loci (*FTO*, *PPARG*, *EXT2*, *JAZF1*, *CDC123-CAMK1D*, *TSPAN8-LGR5*, *ADAMTS9*, and *NOTCH2-ADAM30* in the stage 1 + 2 panel and *THADA* in the stage 1 + 2 + 3 panel). Notably, the originally reported SNPs or those in complete linkage disequilibrium showed the strongest statistical evidence of association in the seven confirmed loci, where the linkage disequilibrium relations and haplotype patterns appear to be similar but not identical between European-descent and Japanese populations (supplementary Figs. S3 and S4).

Besides *KCNQ1* and the 16 candidate loci prioritized here, we investigated the disease association of two candidate gene SNPs—rs734312 in *WFS1* (39) and rs7501939 in *TCF2* (40)—based on the genotype data of our stage 1 panel (n = 1,022) and 964 random control subjects (supplementary Table S6). In some instances, it appeared that the sample size was not sufficient to detect the presumed odds ratio (OR) (supplementary Table S7). Nevertheless, except for rs12779790 in *CDC123-CAMK1D* and rs3740878 in *EXT2*, in the majority of instances, the ORs were consistent with those previously reported. Furthermore, we analyzed seven previously reported SNPs with suggestive evidence of an association in the Japanese population (25), but none attained nominal significance in our first-stage scan (supplementary Table S8).

Ethnic differences in genetic effects on type 2 diabetes. With regard to the candidate gene SNPs robustly confirmed in GWA studies conducted on Japanese and European-descent populations, we compared the risk allele frequency and OR between the meta-analysis dataset of the Japanese population and that of populations of European descent (8–10) (Fig. 3). The OR was consistently higher in the Japanese population for all SNPs except rs5219 in *KCNJ11*. Among the confirmed loci, *CDKAL1*, *CDKN2A/CDKN2B*, *SLC30A8*, and *HHEX* showed a significant difference in the ORs between European-descent and Japanese populations ($P < 0.05$, Woolf's test) (supplementary Table S6). However, the risk allele frequency fluctuated between the two ethnic groups, and the strength of association differed accordingly; this is because an SNP with an risk allele frequency of ~0.5 and a higher OR can give rise to stronger association signals. Thus, whereas *TCF7L2* was shown as the strongest susceptibility locus in populations of European descent (41), its association is estimated to be much weaker in the Japanese population because of the low risk allele frequency. In contrast, the results of the meta-analysis showed that the *CDKN2A/CDKN2B* and *CDKAL1* loci had the strongest associations in the Japanese population;

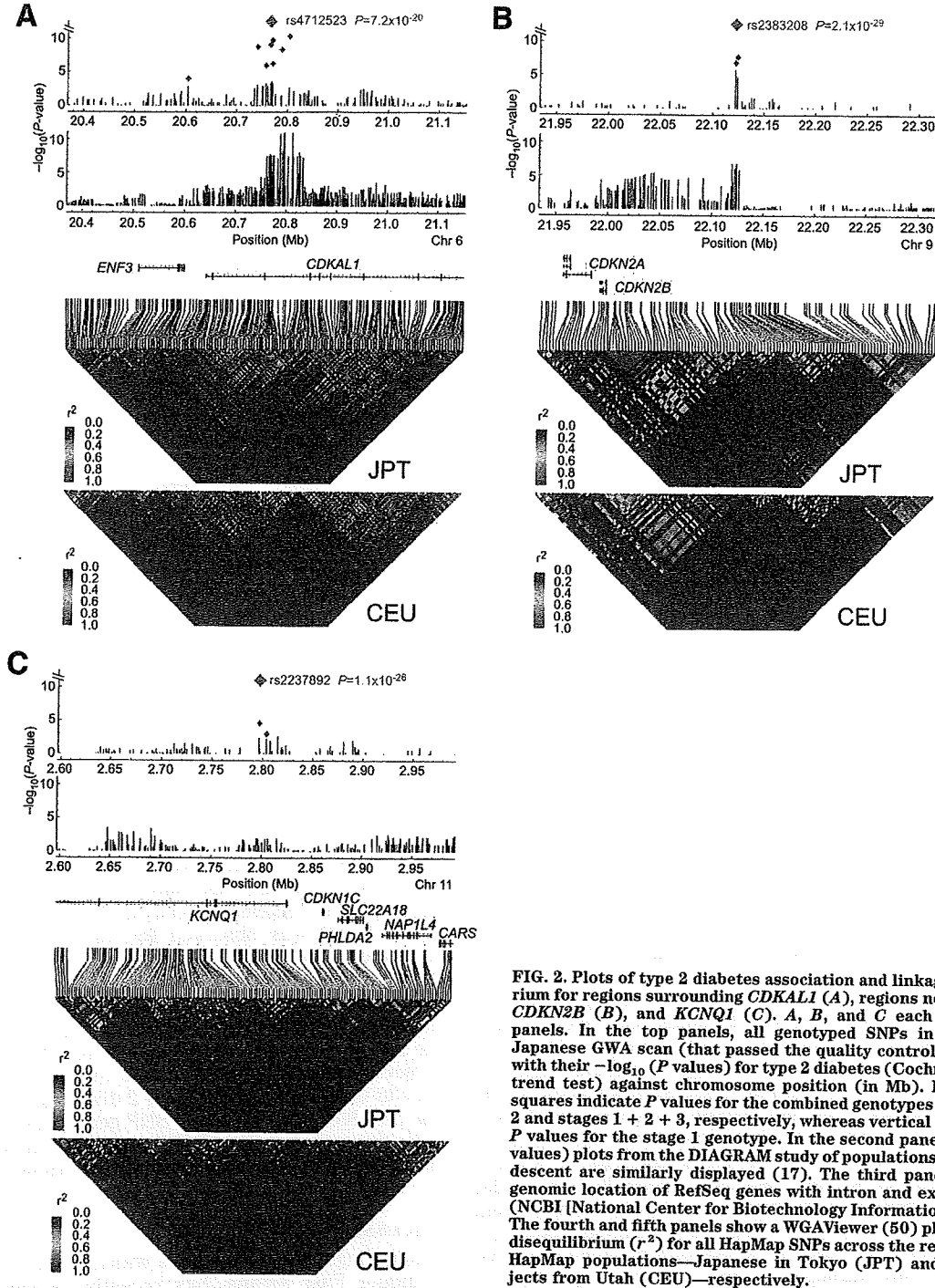

FIG. 2. Plots of type 2 diabetes association and linkage disequilibrium for regions surrounding *CDKAL1* (*A*), regions near *CDKN2A/CDKN2B* (*B*), and *KCNQ1* (*C*). *A*, *B*, and *C* each contain five panels. In the top panels, all genotyped SNPs in the current Japanese GWA scan (that passed the quality control) are plotted with their $-\log_{10}$ (*P* values) for type 2 diabetes (Cochran-Armitage trend test) against chromosome position (in Mb). Blue and red squares indicate *P* values for the combined genotypes of stages 1 + 2 and stages 1 + 2 + 3, respectively, whereas vertical bars indicate *P* values for the stage 1 genotype. In the second panels, $-\log_{10}$ (*P* values) plots from the DIAGRAM study of populations of European descent are similarly displayed (17). The third panels show the genomic location of RefSeq genes with intron and exon structure (NCBI [National Center for Biotechnology Information] Build 35). The fourth and fifth panels show a WGAViewer (50) plot of linkage disequilibrium (r^2) for all HapMap SNPs across the regions for the HapMap populations—Japanese in Tokyo (JPT) and CEPH subjects from Utah (CEU)—respectively.

indeed, we obtained the highest number of hits for these loci.

Next, we compared the strength of association for the seven confirmed loci between Japanese and European-descent populations and calculated R^2 as the proportion of phenotypic variance explained by an SNP (see RESEARCH DESIGN AND METHODS). In Fig. 3, we illustrate the curves corresponding to $R^2 = 0.008$, 0.004, and 0.002, for which the total sample size of case and control subjects required to attain 80% power is $n = 4{,}300$, 8,600, and 17,200 at a significance level of $P = 5 \times 10^{-7}$ (which is the significance threshold generally required in GWA tests), and $n = 1{,}000$, 2,000, and 3,900 at a level of $P = 0.05$. Based on R^2 measurements using the meta-analysis data, the associations of five of seven replicated loci are stronger in the Japanese population than in populations of European descent. For the *CDKAL1* locus, for example, one-fourth of the sample size necessary in populations of European descent is

TABLE 1
Type 2 diabetes susceptibility loci identified or tested for replication in the current Japanese study

rs no.*	Chromosome	Position (bp)	Region	Risk allele/ nonrisk allele	Control risk allele proportion	Stage 1 + 2 (1,629 case subjects/1,517 control subjects)	
						OR (95% CI)	*P* trend
Identified in this GWA scan							
rs4712523	6	20,765,543	*CDKAL1*	G/A	0.407	1.38 (1.25–1.52)	8.0E-10
rs2383208	9	22,122,076	*CDKN2A/B*	A/G	0.553	1.31 (1.18–1.45)	1.6E-07
rs2237892	11	2,796,327	*KCNQ1*	C/T	0.594	1.25 (1.13–1.39)	2.3E-05
rs10425678	19	38,669,236	*PEPD*	C/T	0.261	1.23 (1.10–1.37)	3.6E-04
Replication of previously-reported SNPs							
rs10923931	1	120,230,001	*NOTCH2-ADAM30*	T/G	0.020	1.17 (0.83–1.65)	0.3821
rs7578597	2	43,644,474	*THADA*	T/C	0.990	1.95 (1.03–3.67)	0.0392
rs1801282	3	12,368,125	*PPARG*	C/G	0.969	1.00 (0.75–1.34)	0.9741
rs4607103	3	64,686,944	*ADAMTS9*	C/T	0.594	1.09 (0.99–1.21)	0.0902
rs4402960	3	186,994,389	*IGF2BP2*	T/G	0.310	1.15 (1.04–1.28)	0.0098
rs7754840	6	20,769,229	*CDKAL1*	C/G	0.392	1.42 (1.28–1.57)	1.7E-10
rs7756992	6	20,787,688	*CDKAL1*	G/A	0.448	1.35 (1.23–1.50)	4.6E-09
rs864745	7	27,953,796	*JAZF1*	T/C	0.789	1.08 (0.95–1.22)	0.2456
rs13266634	8	118,253,964	*SLC30A8*	C/T	0.570	1.18 (1.06–1.30)	0.0015
rs10811661	9	22,124,094	*CDKN2A/B*	T/C	0.555	1.35 (1.21–1.49)	2.2E-08
rs12779790	10	12,368,016	*CDC123-CAMK1D*	G/A	0.151	0.98 (0.85–1.13)	0.7984
rs1111875	10	94,452,862	*HHEX*	C/T	0.275	1.19 (1.07–1.33)	0.0011
rs7903146	10	114,748,339	*TCF7L2*	T/C	0.035	1.42 (1.10–1.84)	0.0073
rs5219	11	17,366,148	*KCNJ11*	T/C	0.355	1.22 (1.09–1.35)	2.5E-04
rs3740878	11	44,214,378	*EXT2*	A/G	0.633	1.01 (0.91–1.12)	0.8849
rs7961581	12	69,949,369	*TSPAN8-LGR5*	C/T	0.202	1.12 (0.99–1.27)	0.0751
rs8050136	16	52,373,776	*FTO*	A/C	0.203	1.11 (0.98–1.26)	0.0915

Continued on following page

sufficient to obtain the same level of statistical significance in the Japanese population. This is true for *CDKN2A/CDKN2B*, *HHEX*, and *SLC30A8*, in which <50% of the sample size seems to be sufficient for significance in the Japanese population. However, *TCF7L2* shows an opposite trend in this regard.

Combined genetic risk of type 2 diabetes. Despite the small value of explained variance (R^2) at each risk locus, it is assumed that knowledge about multiple-risk loci could allow us to identify individuals with accumulated genetic risk (42). To this end, a GWA study in Finns (10) investigated the combined risk of type 2 diabetes based on 10 associated loci by logistic regression analysis of the resampled dataset. The total variance explained by 10 loci in Finns is $R^2 = 0.030$, which is equivalent to the value for 7 loci obtained here (see DISCUSSION). Likewise, in a simulated population, we arranged the individuals in the order of the risk estimated by logistic regression, sorted them into 20 equal-sized groups (5% in each), and calculated the actual proportion of affected individuals in each group. We found a 3.7-fold variation in type 2 diabetes prevalence from the lowest to highest estimated risk groups for the combination of seven associated loci in our study (Fig. 4). The receiver operating characteristic curve was also depicted for the combined SNPs as a measure of sensitivity and specificity (supplementary Fig. S5).

Moreover, for risk assessment in the general population, we performed multiple regression analysis using A1C as a surrogate quantitative phenotype to estimate the unbiased effect size of individual loci (supplementary Table S9) and evaluated the combined risk from multiple loci in 12,569 population-based samples (Table 2 and supplementary information). Then, the estimated risk was compared with the actual A1C value and the disease classification of diabetes or pre-diabetes (supplementary information). In the multiple regression analysis, significant association ($P < 0.005$) was observed for all seven loci tested in accordance with the results for the case-control study (Table 1 and supplementary Table S4). As shown in Fig. 4, 5% of male subjects with the highest estimated risk are 2.3 times more likely to suffer from diabetes than those with the lowest estimated risk; the risk is 5.2 times in female subjects, indicating the potential existence of sex difference in the genetic risk of type 2 diabetes (supplementary Fig. S6). Moreover, notably, SNP genotypes alone exerted more exaggerated effects on the increase in genetic risk in diabetes compared with pre-diabetes (Table 2).

DISCUSSION

Conducting GWA studies on a wider range of populations, including East Asians, has recently gained importance because of the discovery of new type 2 diabetes susceptibility variants mapping to the *KCNQ1* gene simultaneously reported in two Japanese studies (25,26). Both studies were, however, initiated some years ago, and they are, by current standards, considered to be modest with regard to the coverage of common SNPs (21 and 56% in HapMap) and number of case subjects (187 and 194 subjects, respectively) in the first-stage scan. Therefore, we conducted another GWA study on the Japanese population with greater coverage of common SNPs (87% of all phase

TABLE 1
Continued

Stage 3 (4,000 case subjects/4,889 control subjects)†		All combined (5,629 case subjects/6,406 control subjects)†		OR (95% CI) reported in Europeans (14,586 case subjects/17,968 control subjects)
OR (95% CI)	*P* trend‡	OR (95% CI)	*P* trend	
1.23 (1.16–1.30)	4.0E-12	1.27 (1.21–1.33)	7.2E-20	1.12 (1.08–1.16)
1.33 (1.26–1.42)	4.8E-22	1.34 (1.27–1.41)	2.1E-29	1.20 (1.14–1.25)
1.36 (1.28–1.45)	8.0E-23	1.33 (1.27–1.41)	1.1E-26	1.18 (1.03–1.33)§
1.10 (1.03–1.18)	0.0020	1.14 (1.07–1.20)	1.4E-05	1.03 (0.97–1.09)§
—	—	—	—	1.13 (1.08–1.17)‖
0.98 (0.73–1.31)	0.55	1.13 (0.87–1.47)	0.35	1.15 (1.10–1.20)‖
—	—	—	—	1.14 (1.08–1.20)
—	—	—	—	1.09 (1.06–1.12)‖
1.14 (1.07–1.21)	2.5E-05	1.14 (1.08–1.21)	1.0E-06	1.14 (1.11–1.18)
—	—	—	—	1.12 (1.08–1.16)
—	—	—	—	1.26 (1.18–1.34)§
—	—	—	—	1.10 (1.07–1.13)‖
1.24 (1.17–1.31)	5.8E-13	1.22 (1.16–1.28)	1.8E-14	1.12 (1.07–1.16)
—	—	—	—	1.2 (1.14–1.25)
—	—	—	—	1.11 (1.07–1.14)‖
1.21 (1.13–1.29)	2.6E-09	1.21 (1.15–1.28)	6.7E-12	1.13 (1.09–1.17)
1.59 (1.38–1.83)	5.3E-11	1.54 (1.36–1.74)	7.6E-12	1.37 (1.31–1.43)
1.02 (0.96–1.08)	0.3008	1.07 (1.01–1.13)	0.0149	1.14 (1.10–1.19)
—	—	—	—	1.20 (1.11–1.30)¶
—	—	—	—	1.09 (1.06–1.12)‖
—	—	—	—	1.17 (1.12–1.22)

Results for one SNP each selected from the individual chromosomal regions in the GWA scans are shown in the table (see supplementary Table S4 for details and supplementary Table S5 for the results of logistic regression adjusted for BMI). The final *P* value was assessed by pooling genotype counts for each SNP from all stages tested (without including 964 random control subjects from GeMBDJ). In two regions, chromosome 6p22.3 (*CDKAL1*) and 19p13 (*PEPD*), the haplotype class showed more significant association than the individual SNP (see supplementary Information). *In the stage 3 panel, we genotyped rs4712523 instead of rs7754840 ($r^2 = 0.96$) or rs7756992 ($r^2 = 0.65$) in CDKAL1, and rs2383208 instead of rs10811661 ($r^2 = 0.89$) near CDKN2A/B, with the aim of determining the SNP(s) with the strongest association in the Japanese population. †In stage 3 of the replication study on previously reported SNPs, after the confirmation of significant association in 4,000 case subjects and 4,889 preselected control subjects, we further characterized 7,680 subjects (who comprised the rest of the 12,569 population-based samples) (see RESEARCH DESIGN AND METHODS and Fig. 1). Thus, for the corresponding SNPs, 5,395 control subjects were reselected from the entire population-based samples and used for the final association analysis in stage 3, which increased the total number of control subjects across the three stages to 6,912. ‡One-tailed test for association was performed in the direction consistent with stage 1 + 2 data; §for 4,549 case and 5,579 control subjects derived from the DIAGRAM consortium of Zeggini et al. (17); ‖for ~60,000 total samples from Zeggini et al. (17); ¶for 3,278 case and 3,508 control subjects from Sladek et al. (6).

1 + 2 HapMap variants [MAF ≥0.05] in CHB (Chinese in Beijing) + JPT (Japanese in Tokyo) and a larger number of case subjects (519 subjects) and unaffected control subjects (503 subjects) in addition to random control subjects in the first-stage scan. Four loci (three previously reported and one novel) were identified via the multistage scans. For the top three loci (*KCNQ1*, *CDKN2A/CDKN2B*, and *CDKAL1*) the OR (>1.25) and MAF (0.41–0.45 in the control subjects) were higher in the Japanese population than in populations of European descent. In addition to the nomination of four susceptibility loci (*KCNQ1*, *CDKN2A/CDKN2B*, *CDKAL1*, and *PEPD*), the current study replicated the significant association of five other loci (*TCF7L2*, *IGF2BP2*, *SLC30A8*, *HHEX*, and *KCNJ11*) previously reported in populations of European descent (6–17) and provided an unbiased estimate of the risk from the confirmed disease genotype.

Empirical studies suggest that the genetic effects of individual causal risk alleles underlying complex genetic diseases such as type 2 diabetes are modest, with most genotype relative risks in the range of 1.1–2.0 (43). Indeed, we observed this to be true for loci that were robustly implicated in the development of type 2 diabetes by GWA scans and/or extensive candidate gene approaches in populations of European descent. Currently, the number of loci has increased to almost 20 (as listed in supplementary Table S6), and in most cases, except for *TCF7L2* and *KCNQ1*, the OR is estimated to be between 1.09 and 1.20.

The current study provides, via genome-wide exploration and replication analysis of some a priori selected loci, significant evidence for the overall tendency toward a stronger association in Japanese rather than European-descent populations at least for alleles with a cosmopolitan effect. The tendency for higher OR in Asians than in Europeans was previously reported for the *CDKAL1* locus (22). Currently, it remains unknown whether the penetrance for a genotype of interest differs considerably between Japanese and European-descent populations. With regard to genetic effects, four of seven confirmed loci have demonstrated significantly higher OR in the Japanese population ($P = 4.1 \times 10^{-5}$ to 0.024) (supplementary Table S6). To simplify the situation, we have further assessed the strength of association for individual SNPs by measuring R^2, which is scaled against OR and risk allele frequency in

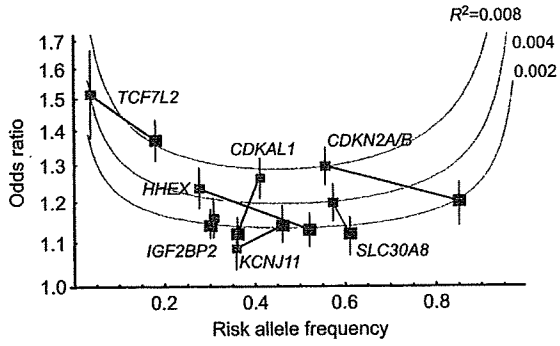

FIG. 3. Comparison of the strength of association for seven confirmed type 2 diabetes loci between Japanese and European-descent populations. For the Japanese population, we estimated ORs and their 95% CIs (red solid squares and vertical lines, respectively) for each locus based on our meta-analysis involving four Japanese case-control studies (supplementary Fig. S2). For populations of European descent, on the other hand, the corresponding values (blue solid squares and vertical lines) were derived from the published data (8–10). The association of an SNP with type 2 diabetes is measured by the coefficient of determination (R^2), which represents the ability to detect association signals using the Cochran-Armitage trend test.

Fig. 3. We found that despite the limited number of SNPs tested here, the same level of statistical significance is often detectable in the Japanese population with a much smaller sample size than that in populations of European descent (supplementary Table S7). Theoretically, the stringency of ascertaining control subjects could lead to some bias in effect size (44). In this respect, in addition to the multistage case-control study, an extensive analysis of associated loci in the general population was conducted, which is the strength of the current study. We used the population-based samples (n = 12,569) in stage 3 to

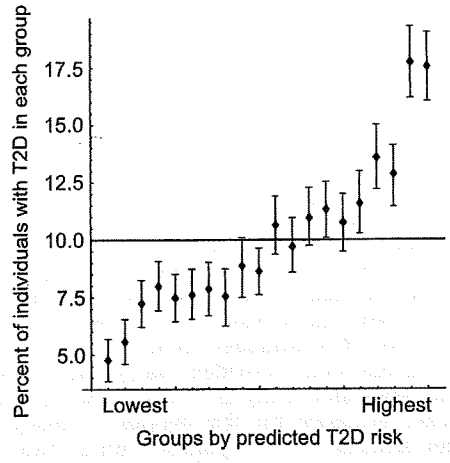

FIG. 4. Estimation of the increase in type 2 diabetes risk from the combination of seven susceptibility variants previously identified and robustly replicated in the current study. We used case and control subjects with complete data from all stages of our study (n = 12,105). First, the risk for the genotypes of an SNP was estimated by logistic regression. Then, the multilocus risk for an individual was assessed as the sum of the risks for his/her genotype at seven SNPs. We simulated a population with 10% prevalence by bootstrap sampling. In the simulated population, we arranged the individuals in the order of their multilocus risk, sorted them into 20 equal-sized groups, and calculated the actual prevalence in each group. Means and 95% CIs of the groupwise prevalence were estimated based on 1,000 bootstrap sampling trials and are plotted in the figure. No significant gene-gene interaction was observed between the seven SNPs by multiple logistic regression analysis. T2D, type 2 diabetes.

investigate the effect of control selection criteria on OR in a case-control comparison and found that the ORs in our meta-analysis were almost comparable to those estimated in the general Japanese population (supplementary Table S10). Moreover, with regard to ethnic diversity, linkage disequilibrium in *CDKAL1* and *KCNJ11* is stronger in East Asians (JPT + CHB), whereas linkage disequilibrium in *IGFBP2* and *HHEX* tends to be stronger in Europeans (CEU [Centre d'Etude du Polymorphisme Humain (CEPH) subjectsfrom Utah]) (Supplementary Figure S4); thus, besides the issue of power, the results of the GWA scans in the Japanese population (or East Asians) seem to be useful in terms of interethnic comparison of association signals, which may enhance the power of fine-mapping efforts designed to identify the causal variants (45).

The tendency of stronger genetic association in the Japanese population is also supported by the concomitant evaluation of multilocus effects. When assuming an additive model, the combined risk of type 2 diabetes can be measured by the sum of the R^2 values of individual loci. For example, the total variance explained by the seven loci depicted in Fig. 3 is 0.030 in the Japanese population and 0.018 in populations of European descent. It remains unknown whether these findings reflect higher heritability of type 2 diabetes in Japanese than in European-descent populations. Because little data are available on the estimation of heritability in the Japanese or East Asian populations, further studies are required to obtain the standardized measures of heritability across different populations by taking into account potential sources of heterogeneity, such as the degree of westernization of lifestyle.

Suggestive evidence of association was identified for SNPs in the *PEPD* gene. *PEPD* plays an important role in collagen metabolism, and some extracellular matrix constituents such as collagen IV have been shown to have a profound impact on insulin secretion (46). Moreover, enhanced collagen degradation via *PEPD* activity has been reported in diabetic patients (47). Although there is evidence suggestive of association at *PEPD* in all three stages, the current GWA study by itself could not confirm or refute the evidence; no significant association was found in the previously reported Diabetes Genetics Replication and Meta-Analysis (DIAGRAM) data from Europeans (risk allele frequency = 0.52, OR = 1.03) (Table 1) and in the initial screening data of the JSNP (Japanese Single Nucleotide Polymorphisms) scan in the Japanese population (187 casevs. 752 random control subjects; P = 0.18 at rs2241380, which is in complete linkage disequilibrium with rs10425678 in *PEPD*; r^2 = 1.0) (25).

The number of genes that could account for an appreciable population-attributable fraction of common diseases is under debate (48). Although the current study detected and/or replicated a total of nine susceptibility loci, including *PEPD* in the Japanese population, a substantial number of SNPs showing some extent of association signals in the first-stage scan remain to be investigated, as reflected by the wide distribution of replicated SNPs with unexamined "gaps" in the lower-left part of the Q-Q plot (supplementary Fig. S7). The ORs corresponding to such unexamined SNPs mostly fall in the range of 1.10–1.25. To assess the statistical power in our GWA scan, we simulated the frequency at which a disease-associated SNP could surpass the cutoff level of the first two stages (stages 1 and 2) (supplementary information and supplementary Table S11). In the current experimental setting, it is likely that >50% of the susceptibility loci

TABLE 2
Combined risk of diabetes and pre-diabetic status based on seven confirmed loci, age, BMI, and sex in the general Japanese population

		Diabetes		Pre-diabetes		Diabetes + Pre-diabetes	
	A1C (%)	RR versus population average (95% CI)	Prevalence	RR versus population average (95% CI)	Prevalence	RR versus population average (95% CI)	Prevalence
Male							
Whole population	5.29 ± 0.88	1.00	0.16	1.00	0.07	1.00	0.23
Highest risk group (5%) assessed by							
All predictors	5.48 ± 0.87	1.65 (1.29–1.97)	0.27	1.34 (0.73–1.83)	0.09	1.56 (1.26–1.78)	0.36
SNP genotypes	5.57 ± 1.12	1.67 (1.32–2.06)	0.27	0.92 (0.44–1.40)	0.07	1.45 (1.16–1.73)	0.34
Age and BMI*	5.44 ± 0.78	1.16 (0.87–1.46)	0.19	1.95 (1.39–2.60)	0.14	1.40 (1.16–1.65)	0.33
Lowest risk group (5%) assessed by							
All predictors	4.98 ± 0.73	0.46 (0.26–0.74)	0.08	0.50 (0.20–0.90)	0.04	0.47 (0.33–0.70)	0.11
SNP genotypes	5.11 ± 0.74	0.72 (0.39–0.92)	0.12	0.71 (0.30–1.10)	0.05	0.72 (0.46–0.86)	0.17
Age and BMI*	4.98 ± 0.77	0.46 (0.30–0.73)	0.08	0.40 (0.10–0.60)	0.03	0.44 (0.27–0.63)	0.10
Female							
Whole population	5.17 ± 0.60	1.00	0.07	1.00	0.06	1.00	0.13
Highest risk group (5%) assessed by							
All predictors	5.55 ± 0.96	3.09 (2.36–3.73)	0.22	2.05 (1.37–2.60)	0.13	2.61 (2.10–2.96)	0.35
SNP genotypes	5.37 ± 0.88	2.30 (1.60–2.78)	0.17	1.17 (0.73–1.80)	0.07	1.78 (1.41–2.10)	0.24
Age and BMI*	5.42 ± 0.78	2.26 (1.71–2.78)	0.16	1.95 (1.34–2.53)	0.12	2.12 (1.73–2.46)	0.28
Lowest risk group (5%) assessed by							
All predictors	4.91 ± 0.43	0.16 (0.00–0.32)	0.01	0.14 (0.00–0.28)	0.01	0.15 (0.04–0.26)	0.02
SNP genotypes	5.02 ± 0.45	0.45 (0.16–0.73)	0.03	0.80 (0.38–1.22)	0.05	0.61 (0.35–0.83)	0.08
Age and BMI*	4.94 ± 0.36	0.24 (0.08–0.64)	0.02	0.19 (0.00–0.37)	0.01	0.22 (0.09–0.47)	0.03

Data are the means ± SD, unless otherwise indicated. Relative risk (RR) is calculated as the ratio of the prevalence in 5% of people with the highest or lowest risk to the prevalence in the whole population. In this study, the combined disease risk for each individual was assessed using the regression for A1C (see supplementary information). Subjects with self-reported diabetes or with A1C ≥6.1 were classified as diabetic, and those who were not under antidiabetic medication and with 5.6 ≤ A1C < 6.1 were classified as pre-diabetic. The actual A1C level and the distribution by diabetic status for each 5% subgroup of the risk group are illustrated in supplementary Fig. S6. *For reference, diabetes and/or pre-diabetes risk was assessed using the participant's age and BMI alone as predictors.

with modest but substantial effects (OR = 1.2–1.3) were unidentified. For example, though not statistically significant, the association of *PPARG* in the Japanese population showed an OR ($P = 0.06$, OR = 1.18 at rs1801282) similar to that in populations of European descent in a meta-analysis, including the current study (supplementary Table S4). Increasing the sample size of the stage 1 panel and/or the number of SNPs genotyped in the second-stage scan would allow us to discover more susceptibility variants, including new population-specific loci, in the Japanese population.

The incidence of type 2 diabetes is escalating to epidemic proportions globally, with a higher acceleration rate in non-European populations (49). The integration of GWA study results, i.e., a meta-analysis (17), for both European-descent and non-European populations is necessary for a comprehensive understanding of the genetics of type 2 diabetes, and it will lead to the efficient use of genomic information based on ethnic diversity in clinical research.

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病院情報システムでのSS-MIX Web参照システムを用いた他院からの紹介データ参照の運用

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Reference of electronic clinical data of introduced patients by SS-MIX web archive viewer on Hospital Information System

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We started using the electronic medical record (EMR) and filmless system (PACS) in the Kyushu University hospital in February 2008. We have distributed about 1,900 EMR terminals and 260 PACS terminals. These terminals have gotten disconnected from external networks including the Internet and prohibited to use external storage devices (CD, USB memory etc) for security purposes. Therefore, we have had problems when we want to refer to the digitalized data brought from other medical institutes on the HIS terminals. Then we introduce the Standardized Structured Medical record Information eXchange (SS-MIX) Web Archive viewer + EX (data formats (.jpg, .doc, .xls, .pdf, etc) other than DICOM and HL7 can be referred as options) in our hospital in February 2009. After CDs from other medical institutes are checked by an antivirus software, we install the digital data in CDs into the server. Then, we can refer to the digital data on the HIS terminal through SS-MIX web archive viewer, and we can copy the contents of digital data into electronic medical record as occasions demand. In this paper, we report our case which shows how to operate the SS-MIX reference system in an university hospital, and how to solve problems.

Keywords: SS-MIX, PDI, DICOM, HL7

1. はじめに

九州大学病院では2008年2月より電子カルテシステム：HIS（日本アイ・ビー・エム株式会社製Venus Ⅲ）、フィルムレスシステム：PACS（富士フイルムメディカル株式会社製Synapse）を導入し、現在約1900台のHIS端末と260台のPACS端末が稼動している。HIS端末ではPACSサーバーに格納されている画像の参照ができ、PACS端末では電子カルテ・オーダーシステムの使用を可能としており、相互のアプリケーションの使用が可能である。これらの端末はセキュリティ上、外部とのネットワーク接続を遮断し、またUSBメモリ、CD・DVD、フロッピ等の外部メディアの使用を不可としている。このことから患者により他の医療施設から持ち込まれた画像・テキストを含む電子データを診察時にHIS端末、PACS端末で参照することができないため、電子カルテシステムとの電子的連携ができないことが問題であった。

そこで本院では、厚生労働省の診療情報交換推進事業であること、HL7 v2.5形式にて格納された処方、注射、検体検査等の診療情報を参照できることなどから、2009年2月より、厚生労働省診療情報交換推進事業SS-MIX Webアーカイブビューア+EX（オプションとしてDICOM、HL7以外の規格も参照可能）を導入し、患者により持ち込まれた電子データにウイルスチェックを行い、診察前にサーバーに取り込み、診察時にWebで参照する運用を開始した。今回、本院におけるシステム運用方法を紹介し、課題の整理と問題解決の方向性について報告する。

2. 方法

本院では、外来受付窓口で患者が他院からの紹介CDを持っていることがわかった場合、診療録管理室外来分室に患者を案内し、診療録管理室外来分室に設備されてあるSS-MIX診療情報提供書CD取り込み端末よりサーバーへ取り込みを行う運用をしている。診療録管理室外来分室では、まず担当者がCDのウィルスチェックを行い、SS-MIX診療情報提供書CD取り込み端末より診療データをサーバーに格納する。SS-MIXアーカイブビューアで取り込めないMS-WORD、EXCEL、PDFなどのDICOM、HL7以外の規格に関しては、紹介状CD（拡張ファイル）取り込みメニューより、サーバーへの取り込みを行っている。そこでウイルスチェックを含む電子データの取り込み作業時間や電子情報の取り込みの可否を考慮し、図1に示す運用を行っている。 格納された診療データは、各HIS端末、PACS端末の医療情報システム上のアイコンからSS-MIXアーカイブビューアの患者検

索画面を立ち上げられるように設定しおり、検索画面からIDを入力することにより、WEBにて画像等を参照できるようになっている。（図2）

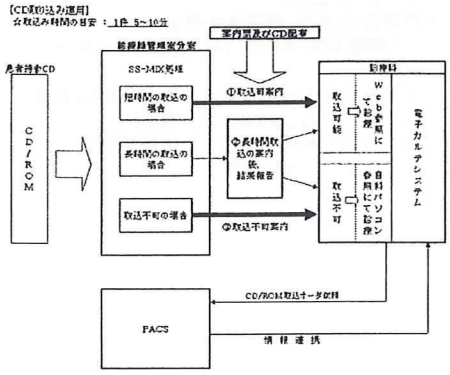

図1 九州大病院におけるCD取り込みの運用方法

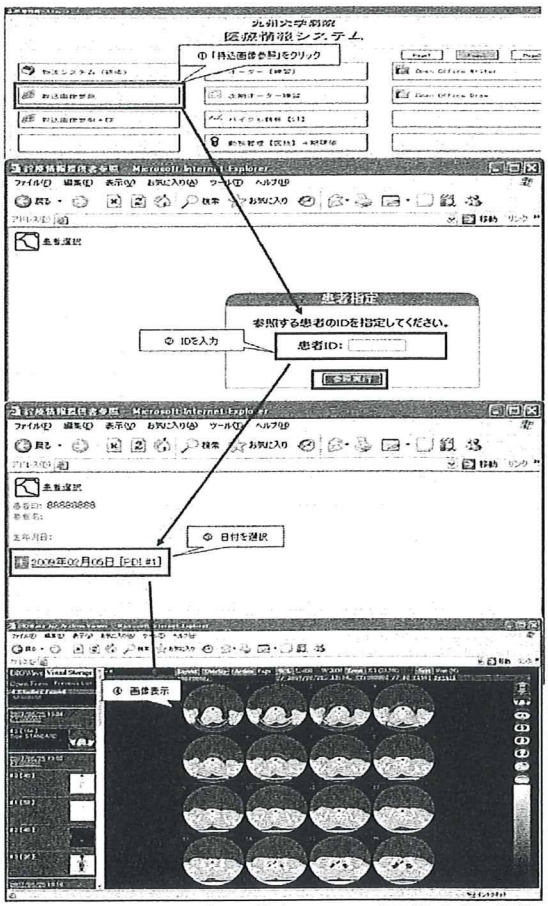

図2 SS-MIXアーカイブビューア　画像参照手順

診療情報提供書CD取り込み端末で取り込めなかったDICOMファイルが含まれたCDに関しては、別途PACSサーバーへのCD取り込みオーダーを出して取り込みを行う運用としている。

3. 結果

2009年2月24日より、SS-MIX Webアーカイブビューア+EXの運用を行った。月別のデータ取り込み数と平均作業時間を表1に示す。2009年2月の運用開始直後は、取り込み作業に不慣れなことや画像参照時のサーバーのトラブルなどがあり、2009年2月の参照可能率が53.8%と低いが、その後作業の効率化も図れ、2009年3月から6月分の参照可能率は平均76.9%、一枚あたりの平均作業時間は、8.5分となっており、徐々に平均作業時間も少なくなり、参照可能率も高くなっている。

また今まで電子カルテシステムに添付できなかったJPEG画像等も、SS-MIX Webアーカイブビューア+EXで参照後、必要に応じて電子カルテへの添付が可能となった。

表1 月別のデータ取り込み数と平均作業時間

	CD持参患者数	CD取込枚数	参照可能数	参照不可数	参照可能率(%)	平均作業時間(分)
2009年2月	24	22	14	8	53.8%	13.7
2009年3月	103	104	73	31	70.2%	7.3
2009年4月	167	181	141	31	77.9%	7.7
2009年5月	148	161	126	35	78.3%	8.8
2009年6月	183	191	155	36	81.2%	10.0

4. 考察

SS-MIX Webアーカイブビューア+EXを導入し運用を行い、下記のような状況が判明した。

①持ち込まれたJPEGなどの電子画像データを診察時に確認でき、電子カルテシステムに画像データを貼付可能となった。

②SS-MIX、IHE PDIに準拠していないCDも多く、取り込み端末でサーバーに取り込めないCDがある。またアーカイブビューアは、現状ではロスレスJPEG画像に未対応のため取り込み後参照できない画像もある。

③サイズの大きいMS-WORD、EXCEL、PPTファイルや数百枚のJPEG画像を提供する医療施設もあり、診察時の参照に時間を要すこともある。また電子カルテシステムに画像を添付するため、HISサーバーの容量を圧迫することも考えられる。

④CT、MRI、PETなど全シリーズを含んだサイズの大きいデータも多く、約6カ月の運用でデータ容量が150GBであった。今後サーバーの容量増設する、もしくは画像の保管期間などを決め一定期間後削除するなどの運用を考える必要がある。

⑤通常1人で取り込み作業を行っているが、毎月CD取り込み枚数も増加し、担当者の作業量が増加している。今後も枚数増加が予想されるため、担当者の増員も視野に入れる必要がある。

そこでこのような状況を踏まえ、本院では下記の運用を検討している。

①参照可能率の問題から持ち込まれたCDのウィルスチェック後、診療録管理室外来分室で取り込みオーダーを出し、PACSサーバーに取り込む。SS-MIXに準

拠した診療情報提供書CDもしくは電子診療データCD、JPEGなどのDICOM、HL7以外の規格は現状通りSS-MIX Webアーカイブビューア+EXで取り込みを行い参照する。
②SS-MIXに準拠した診療情報提供書CDもしくは電子診療データCD、及びIHE PDIに準拠した形式でCD出力してもらうよう地域の医療施設に協力を仰ぐ。
③持ち込みCDを診療録管理室で管理し、サーバーに保管したデータは一定期間後削除する。

今後、持ち込みCD数は益々増加すると思われる。セキュリティの面も考慮しつつ、診療データの連携を効率良く行うためのシステム構築・運用がより一層求められる。

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地域医療連携としての糖尿病

ディジーズマネジメントによる糖尿病地域連携

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