

1st EAST-WEST FORUM

Heterogeneity of Type 2 Diabetes between East and West

SUMMARY

Editors

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Co-sponsored by

Japan Diabetes Society

and

European Association for the Study of Diabetes

OBJECTIVES

Japan diabetes Society (JDS) and European Association for the Study of Diabetes (EASD) jointly held a forum, which was aiming at understanding the differences in type 2 diabetes between Europe and Asia, and to provide a foundation from which young researchers could start making clinical collaborations.

DATE AND TIME

Saturday, May 29th, 2010, 14:15-17:00

VENUE

Hotel Granvia Okayama, Japan
1-5 Kita-kuEkimoto-cho, Okayama 700-8515 Japan

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ACKNOWLEDGEMENTS

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(by alphabetical order)

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President of the 53rd Annual Meeting of the Japan Diabetes Society

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Dr. Ulf Smith

President, EASD

WELCOME ADDRESS

Dr. Kohei Kaku

President of the 53rd Annual Meeting of the Japan Diabetes Society

Professor, Division of Diabetes, Endocrinology and Metabolism

Kawasaki Medical School, Okayama, Japan



It is a great honor and pleasure for me to present the Welcome Address at the first East West Forum. The major purpose of this forum is to promote mutual understanding between the EASD and JDS. As we are all critically aware, the number of people of diabetes is now increasing globally, making this a truly worldwide issue that needs to be urgently solved. In order to overcome this pervasive disease, it is now time to fully share the latest knowledge regarding the etiology and pathophysiology of the disease between all nations and races. Needless to say, the cultures, lifestyles, and ways of thinking are not always similar, with differences particularly evident between Western and Eastern countries. But I believe that frank and earnest discussions are extremely productive, helping to make a huge contribution toward establishing a close working relationship and deep friendship between the EASD and JDS. Therefore we should concentrate our energy on

ensuring that this forum, which is held in conjunction with the 53rd Annual Meeting of the Japanese Diabetes Society, looks forward to a brilliant and successful future. I am very proud to sponsor the first forum in Okayama, Japan and urge all participants to make the most of this marvelous opportunity to mix with their fellow attendees, working together to make this first East West Forum a major success.

OPENING ADDRESS

Dr. Takashi Kadowaki

President of the Japan Diabetes Society

Professor, Department of Metabolic Diseases, Graduate School of Medicine

The University of Tokyo, Tokyo, Japan



I would like to extend my cordial welcome to all the participants in this first East West Forum. The Japan Diabetes Society has been emphasizing the need for international collaboration to combat the worldwide problem of diabetes, and with this in mind has been forming close working ties with the IDF, ADA, EASD, and AASD. I would like to take this opportunity of using my address to the forum as President of the JDS to put even greater emphasis on this need for international collaboration, given the worldwide epidemic of diabetes. In this regard it should be noted that Caucasian, or European-type diabetes, and Asian-type diabetes, while having some similarities also have important differences, in genetics, pathophysiology, and clinical phenotypes, all of which will be discussed in detail in this forum. In order to facilitate understanding these similarities and differences between diabetes in Europe and Asian patients, an understanding that is essential for an effective scientific-based fight

against diabetes, the EASD and JDS have decided to embark on this special initiative, namely the East West Forum. It is my sincere hope that this first East West Forum will be extremely valuable, opening a long lasting dialogue and friendship between the EASD and JDS as well as helping to initiate productive research collaboration, especially among young researchers between European and Asian countries. In closing, I'd like to express my sincere gratitude to Prof. Ulf Smith, the president of the EASD, and Prof. Edwin Gale, editor in chief in *Diabetologia*, as well as Prof. Tajima of the Japan Diabetes Society, who is in charge of international affairs, who together really made this historically important forum possible.

LECTURES

Co-chairs: Dr. Edwin Gale, *University of Bristol, UK*
Dr. Naoko Tajima, *Jikei University, Japan*

INTRODUCTION



Prof. Naoko Tajima explained how the forum was started, and noted that its aim was to promote better understanding of the similarities and differences in etiology, pathophysiology, clinical phenotypes, clinical care, and epidemiology in diabetes between Europe and East Asia. Prof. Edwin Gale thought the Forum would provide a welcome opportunity to study the apparent differences between the pattern of diabetes in Western and Eastern countries. He was looking forward to establishing practical working collaborations to try and identify questions that the East and West can work on together.

Naoko Tajima: Good afternoon ladies and gentlemen, dear colleagues, my name is Naoko Tajima of the Jikei University School of Medicine, Japan, and Prof. Edwin Gale of University of Bristol, UK. will co-chair the lectures with me.

Firstly I would like to explain how this forum started. In October 2009, during EASD Vienna congress, Prof. Ulf Smith, the president of the European Association for the Study of Diabetes, and Prof. Edwin Gale, editor-in-chief of *Diabetologia*, Prof. Takashi Kadowaki, the president of the Japan Diabetes Society, and myself, executive director of JDS and responsible for international affairs, have met and discussed the future collaborative activities between EASD and Japan Diabetes Society.

The plan was approved by the two organizations, and today the first forum is going to be held as the official program of the 53rd Annual Scientific Meeting of the Japan Diabetes Society. We really appreciate Prof. Kohei Kaku for his kind understanding to include this session in the Congress program.

The aim of this forum is to promote better understanding of the similarities and differences in etiology, pathophysiology, clinical phenotypes, and clinical care, and epidemiology in diabetes between Europe and East Asia. We wish that this forum will develop to the activities such as joint symposia, exchanging program of the researchers, and collaborative studies. In addition, this forum intends to foster young investigators through exchanging programs. Now, Prof. Gale will give the details of this session.

Edwin Gale: Dear colleagues, it's an enormous pleasure to be here today. We are at the end of your meeting, but I hope at the beginning of a very fruitful collaboration between our society, the EASD, and your own society here. A writer for my country once said that, East is East, and West is West, and never the two shall meet. But that was 100 years ago, and we have been meeting since then. But I think most people in this room would agree there are challenging apparent differences between the pattern of diabetes in Westerners and in your own country. We see the same mechanisms, but perhaps these mechanisms are filtered through a different culture, different lifestyle, a different genetic background. And so there are very teasing similarities, but also differences between the pattern of clinical diabetes in Europe and in Japan.

And that is why we want to start this meeting, looking if you like at comparative diabetes. And we wanted to make this a practical collaboration, not just a meeting where we spoke, but also we want to establish practical working collaborations to try and identify questions that we can work on together. And as Dr. Tajima said, we have a particular interest in fostering and encouraging young investigators to work in Europe and Japan, to share knowledge, and to work on the same problems.

So that is the name of the East West Forum. And I also thank Professors Kaku, Kadowaki, and others, including Prof. Smith, who have made this possible.

1: EPIDEMIOLOGY

L-1 Epidemiology of type 2 diabetes in European populations

Dr. Markku Laakso

Department of Medicine, University of Eastern Finland, Kuopio, Finland



The epidemic of type 2 diabetes is among the most important challenges for healthcare systems in the next decades in Europe. The health consequences of obesity include type 2 diabetes, atherosclerosis, heart failure, and more. Obesity is the driving force behind increases in the incidence and prevalence of type 2 diabetes in European populations. Among risk factors for type 2 diabetes, modifiable risk factors are excess body weight, physical inactivity, high-fat and low-fiber diets, and tobacco smoking. Non-modifiable risk factors are family history (genes), age, urbanization, ethnicity, and low birth weight. There are currently more than 230 million people with diabetes worldwide; the number will exceed 350 million by 2025. In 2003, the five countries with the largest numbers of persons with diabetes were India (35.5 million), China (23.8 million), the United States (16 million), Russia (9.7 million) and Japan (6.7 million). By 2025, the number of people with diabetes is

expected to more than double in Africa, the Eastern Mediterranean, the Middle East, and South-East Asia. Modification of life-style factors (weight loss, healthy diet, physical activity) is the only rational treatment for the prevention of obesity and type 2 diabetes.

L-2 Epidemiology of type 2 diabetes in Asian populations

Dr. Naoko Tajima

Jikei University School of Medicine, Tokyo, Japan

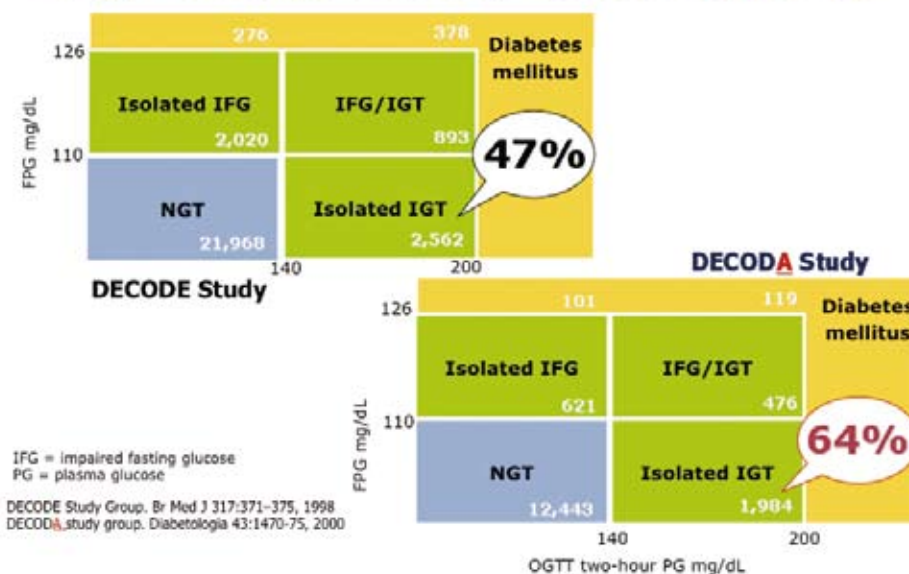


Last year, the IDF updated the Diabetes Atlas and reported estimates of prevalence of type 2 diabetes for both 2010 and 2030. Overall, in many Asian countries, the prevalence rate itself is less than 10%, with the comparative prevalence being 4.7%. However, we should realize that the scope of the problem in this region is indeed large. Because, 1) this region contains some of the most populated countries in the world, with China accounting for 20% of the world population, 2) a rapid lifestyle change or urbanization in this region, suggests a large pool of people at substantial risk of developing diabetes, 3) Asians tend to develop diabetes with a lesser degree of obesity than Caucasians and 4) people in some Western Pacific countries tend to develop diabetes at a younger age, with most people with diabetes aged between 45 and 64 years.

To overcome a rapid increase in number of diabetes, early detection of this disorder is critical. Both in the East and West, the first sign of dysglycemia is the 2- hour glucose value after the 75g OGTT or post-prandial hyperglycemia. DECODA study, Asian version of the DECODE study, including approximately 16,000 OGTT results from 11 Asian-origin general population-based studies demonstrates that among pre-diabetes groups 64% of people were categorized as having an isolated IGT. The corresponded figure from the DECODE study was

47%, suggesting that postprandial hyperglycemia may be more prominent in Asian populations than in Caucasians.

A High Percentage of Isolated IGT in DECODA Cohort



In many Asian countries the number of children and adolescents with type 2 diabetes now greatly outnumbers those with type 1 diabetes and has become a global problem. In Japan, a national school health survey was started in 1974 allowing us to accumulate long-term annual incidence data of 2.6/100,000. From 1974 to 2005, approximately 9.3 million children were urine glucose tested and, of these, 243 were diagnosed as having type 2 diabetes. The characteristics of type 2 diabetes among children and adolescents include; a higher incidence in 13- to 15-year-olds than in 6- to 12-year-olds, no sex difference, more than half had a family history of diabetes and 83.4% of these individuals are obese ($\geq 20\%$ overweight). Slowly progressive type 1 diabetes (SPT1D), defined by GAD+ and or 1A-2+, are oftentimes found by the urine glucose testing at school and its annual incidence is 0.57/100,000 (1974-2004). Individuals with SPT1D initially exhibit minimal symptoms without ketosis, a distinct female predominance, an older age of onset in lean individuals, as well as higher HbA1c levels and lower insulin response to oral glucose load than rapid-onset type 1 diabetes.

Epidemiology of T2D in Children as Detected by Urine Glucose Screening at School Tokyo Metropolitan Area

- 9,268,730 examined (6-15 yrs old, 1974-2005): 243 cases of T2D
- Annual incidence rates: 5-year/10⁵

	T2D	SPT1D
1974-80	1.73	0.39
1981-85	3.23	0.88
1986-90	3.05	0.31
1991-95	2.90	0.47
1996-00	2.70	0.92
2001-05	2.50	0.56*

*2001-04

Table 1 - Features of children diagnosed with SPT1D at the time of diagnosis

Total number	54
Males/females	19/35
Age at diagnosis	11.6 ± 2.4 years
Primary school/junior high school students	20/34
BMI	17.5 ± 2.0
Fasting plasma glucose	165 ± 58 mg/dL
HbA1c	9.2 ± 2.6%
Immunoreactive insulin	8.6 ± 4.5 μU/mL
Frequency of positive ICA	33/48 (68.8%)
Frequency of positive anti-GAD antibodies	34/48 (70.8%)

Urakami T, Kitagawa T et al. DRCP 80:473-6, 2008

- Higher incidence in 13-15 year-old (6.73/10⁵) than in 6-12 year-old (0.75/10⁵)
- No sex difference
- 56.5% had family history of diabetes (1st, 2nd degree relatives)
- 83.4% were obese ($\geq 20\%$ overweight)
- SPT1D is usually detected by urine glucose screening at school

Urakami T, Kitagawa T et al. Diabetes Care 28:1876-81, 2005.

Asian people with diabetes are more likely to develop ESRD than Caucasian people. However, in many developing countries these patients cannot afford renal replacement therapy. In Japan, diabetic nephropathy has become the most frequent condition associated with hemodialysis since the late 80's, with the incidence of new dialysis patients increasing linearly, rising to 15,750 in 2007. In addition, the occurrence of cardiovascular complications and associated morbidity and mortality, which previously was very low in Japanese diabetics is now approaching the rates reported in the US and Europe. The Asia-Pacific Collaborative Study has recently reported that among Asian people with diabetes, stroke rather than CHD was the main cause of death among diabetics. In contrast, in Hong Kong and Singapore, the mortality rate associated with stroke was similar or a little lower than that of CHD.

As discussed, there is a large diversity between East and West as well as within East Asian countries in diabetes epidemiology. Therefore, it is very important to accumulate new high-level evidence which will certainly shed light on the problems remained unsolved in the etiology of type 2 diabetes.

Q & A

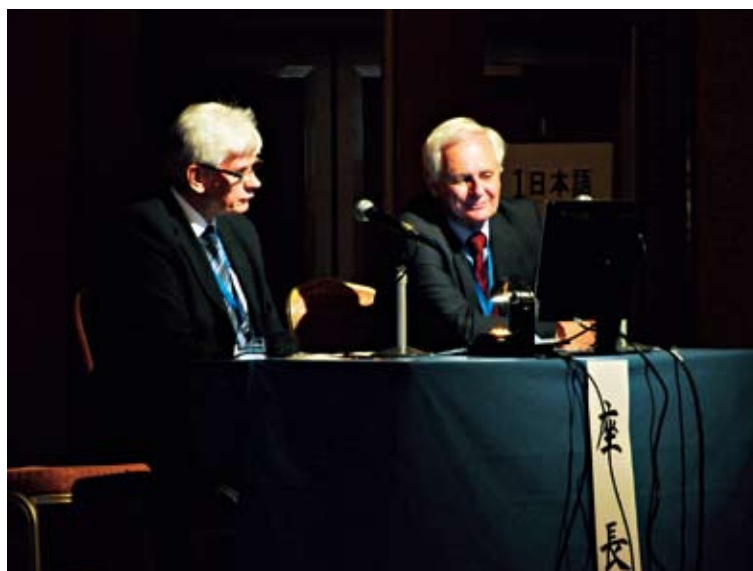
Gale: I will take the Chairman's privilege, and ask both speakers the first question. Is there a difference between European and Japanese type 2 diabetes, and if so, what is the difference?

Laakso: I think that the major difference is the role of obesity. As I showed in my presentation, new and previously diagnosed diabetics in Europe are more obese than corresponding Asian patients. And although it was not really discussed in the presentation, my understanding is that the role of defects in insulin secretion is more pronounced in Asian diabetics, at least based on results from previous studies. Therefore these are the two major differences.

Tajima: In regard to obesity, in Asian countries females are not more obese than males, and this is a huge difference compared to European subjects. In addition diabetes develops at a younger age in Asian subjects, although we don't know the reason for this. And in terms of childhood obesity, the percentage of obese children has decreased slightly in Japan, probably due to improved education in schools on the role of a healthy diet and exercise. Also, a risk of developing micro- and macro complications appears differently between East and West.

Wilfred Fujimoto, University of Washington, Seattle: I think that part of the apparent difference in the relationship between obesity and type 2 diabetes may lie in the definition of obesity used in Europe and Asia. In fact I believe that the criteria for obesity in Asians should be different to that used in Europeans. If this was taken into account, I think it becomes clear that obesity is a major risk factor for type 2 diabetes.

Gale: I think that's a very important point that will be addressed by some of the subsequent speakers.



2: GENETICS

L-3 What we have learned about diabetes from genetics studies in Europeans

Dr. Timothy M. Frayling

Peninsula Medical School, University of Exeter, Exeter, UK



The recent success of genetics identified a lot of common genetic variants associated with type 2 diabetes mellitus. Although not all of them are assigned to single genes (some are even located in intergenic regions), around 20 genetic variants reached genome-wide significance level and are thus considered to be 'true'. However, genetic factors identified so far do not distinguish patients from controls very well; body mass index (BMI) does a much better job. These DNA variants do not provide strong predictive power for the disease.

Because genotype is robust information and less susceptible to bias or confounding effects than other clinical factors, these genes may help in dissecting heterogeneous diseases such as type 2 diabetes by connecting genes to intermediate traits. For example, the FTO gene directly affects adiposity, MTN1RB can modify insulin secretion by the melatonin system and circadian rhythm, and SHBG gene variants contribute to SHBG levels. Thus, we have implicated some new pathways as important in the etiology of diabetes. Lack of association of cytokine genes or 'type 1 diabetes genes' strongly suggests that the autoimmune mechanism may not be involved in the pathophysiology of type 2 diabetes.

So far, most genetic factors show similar effects among the different ethnic groups, although the risk alleles can be at different frequencies. The proportions of Europeans individuals carrying two copies of the "fat allele" at the FTO gene, and those with two copies of the "thin allele" are 16% and 35%, respectively. Although there are controversial reports about the impact of FTO on BMI in Japanese or Chinese, and the risk allele frequency is different from Caucasians, meta-analysis of the studies revealed that FTO alters BMI also in East Asian populations with the same effect size as that seen in Europeans (Fig. 2).

Future directions of research in this field will include whole genome resequencing of patients to identify novel variants causing disease. Dr. Frayling emphasized the importance of the functional analysis of relevant genes.

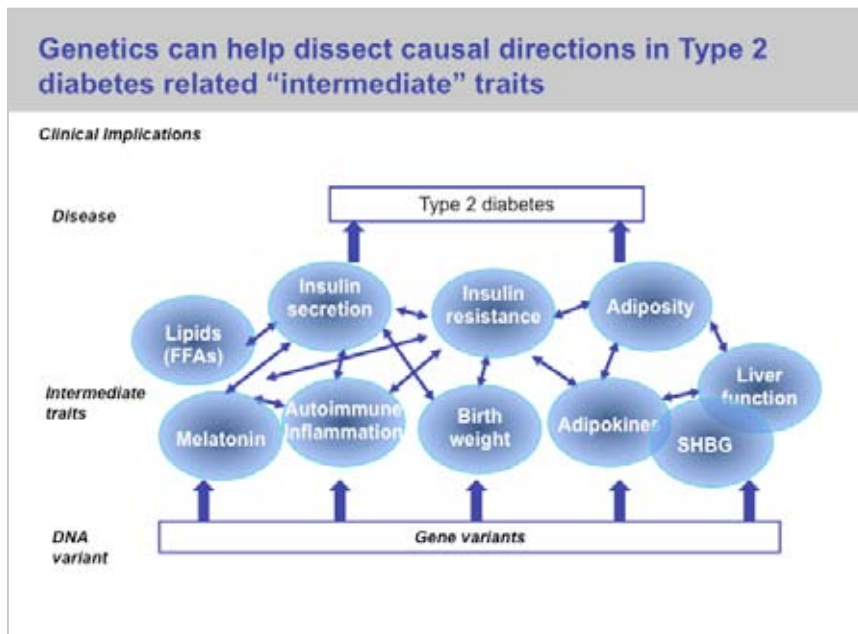


Fig 1

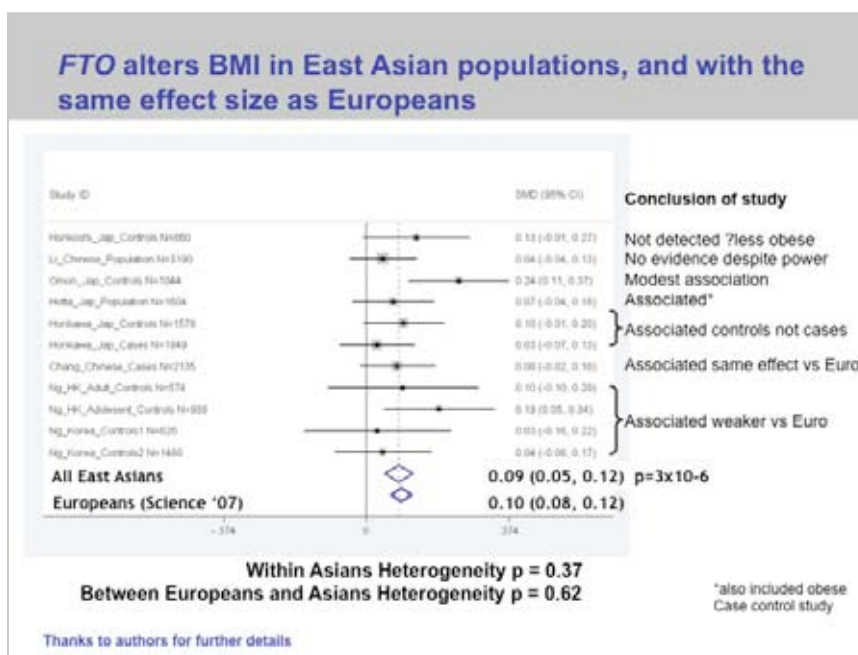
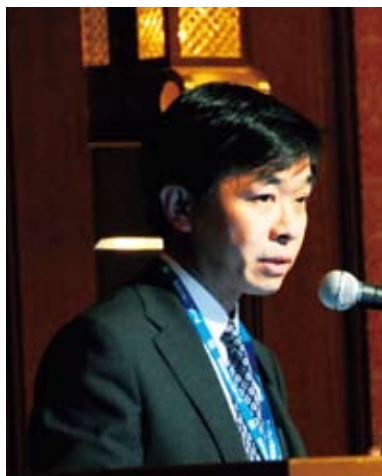


Fig 2

L-4 Genetic factors for type 2 diabetes in Japanese

Dr. Kazuki Yasuda

Director, Department of Metabolic Disorder, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan



Patients with type 2 diabetes in Japan are not so obese as those in Western countries, and the majority exhibit impairment in acute insulin response to glucose load even before the onset of overt diabetes. Therefore it has been postulated that the genetic background for diabetes in the Japanese population may be different from that found in Caucasians.

For "monogenic" type of diabetes, major subtypes of MODY in Japan are MODY1, 3, and 5. A marked reduction of beta cells was seen in autopsy pancreata of patients with mitochondrial diabetes. For "polygenic" types, more than a hundred genes were investigated by candidate gene approach, but rather few have been replicated in multiple ethnic groups. Affected sib-pair analysis in Japanese revealed a chromosome 11p region linked with diabetes, which has not been reported in Caucasians.

In 2008, two independent GWAS projects in Japan found very similar regions of the intron 15 of KCNQ1 gene as conferring disease susceptibility, and this locus proved to be most strongly associated with diabetes in this population. In Caucasians KCNQ1 was also associated with diabetes, but MAFs (minor allele frequencies) are lower.

The functional analysis of susceptibility SNPs discovered by GWAS is generally very difficult, mainly because most SNPs reside in introns or intergenic regions. Dr. Yasuda's group is working to clarify the functional role of KCNQ1 SNPs (Fig 1). A very recent paper from Iceland reported SNPs in the imprinted region spanning the KCNQ1 gene exhibited association with diabetes in a parental origin- specific manner, which indicated interaction of genetics and epigenetics.

So far, most of the diabetes susceptibility genes were universal between East and West, with TCF7L2 and KCNQ1 as the two strongest genes, but the risk allele frequencies and contribution to the disease in each ethnic group are variable. One thing to be pointed out is that a comprehensive GWAS with larger panels in Japanese is necessary to obtain a general picture of common variants associated with the disease.

Japanese researchers including Dr. Yasuda’s group recently reported that a novel and rather rare SNP in *KCNJ15* (rs3746876) is associated with diabetes in the Japanese, and the association seemed specific to East Asians: this SNP has a stronger effect than *KCNQ1* for the lean subtype of diabetes. Such rare variants (including structural variants) with stronger effects may be more specific to each ethnic group, each phenotype, each pedigree, or even each subject. Dr. Yasuda noted that the National Center for Global Health and Medicine established a Diabetes Research Center last April to collect and analyze a variety of clinical resources for diabetes research in Japan, including cases of rare and/or extreme phenotype (Fig. 2).

The possible functions of *KCNQ1* SNP(s)

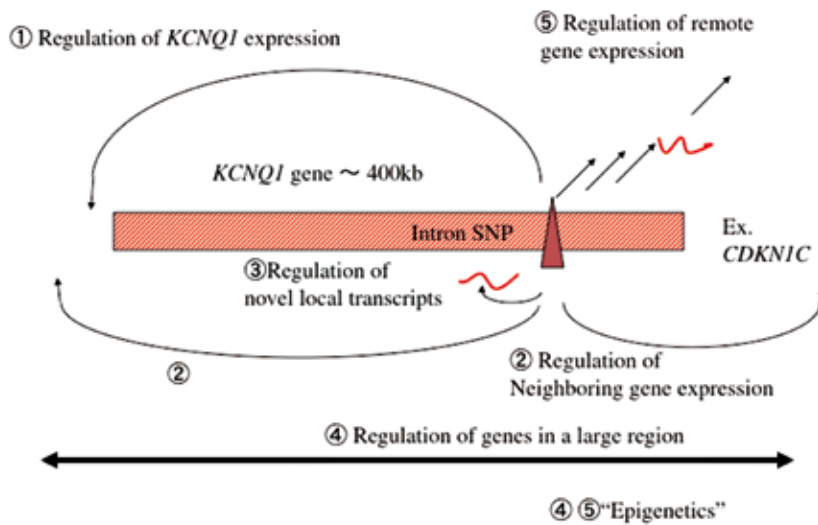


Fig 1



National Center for Global Health and Medicine
(Previously International Medical Center of Japan)



Diabetes Research Center [2010.4~]

Chair: Masato Kasuga
Faculty staffs from hospital & research institute
Collaboration with JDS

- Clinical resources for diabetes research in Japan
 - Type 1 diabetes (Acute, SPIDDM, and Fulminant type)
 - Common type 2 diabetes
 - Cases of rare and/or extreme phenotype
- Multi-omics studies
- Detailed phenotyping
- Molecular analysis and animal models



Molecular basis of pathophysiology of diabetes in Japan
Novel methods of diagnosis & therapeutic targets

Fig 2

3: PATHOPHYSIOLOGY AND CLINICAL PHENOTYPE

L-5 Insulin resistance and obesity in Caucasians

Dr. Ulf Smith

Lundberg Laboratory for Diabetes Research, University of Gothenburg, Gothenburg, Sweden



Hypertrophic obesity is characterized by enlarged adipose cells (mean of several subcutaneous sites), which is related to insulin resistance, dyslipidemia, type 2 diabetes (i.e., the metabolic syndrome and MONO (~25%). In contrast, hypercellular obesity is obesity without adipose cell enlargement (i.e., with increased numbers of fat cells), which is not related to the metabolic syndrome MNBO (10%-30%). Waist circumference is an easy marker of metabolic risk, is used to define the metabolic syndrome, and also correlates positively with adipose cell size. Diabetes risk markedly increases at lower BMI in the East (≥ 24.5 kg/m²) compared to that for the West (~ 28 kg/m²). These data raised the possibility that differences in body fat and its distribution play a role in the increased diabetes susceptibility in the East, and that genetic factors may cause restricted subcutaneous adipogenesis and inappropriate adipose cell enlargement with dysfunctional adipose tissue and ectopic

lipid accumulation (visceral fat, liver fat, etc).

The Diabetes Prevention Program reported that 1) in the placebo and lifestyle groups, visceral adipose tissue at the L2–3 and L4–5 disc spaces, waist/hip ratio, and waist circumference predicted diabetes, 2) no measure predicted diabetes in the metformin group, 3) computed tomography provided no important advantage over these simple measures, and 4) subcutaneous adipose tissue did not predict diabetes (Am J Clin Nutr 87:1212-8, 2008). South Asians who had 25% total body fat exhibited significantly increased abdominal subcutaneous adipocyte size, decreased plasma adiponectin and decreased glucose disposal rate as compared with Caucasians who had almost the same total body fat (Chandalia M et al. PLoS One 2(8):e812, 2007). Juliana Chan and Takashi Kadowaki together with other co-authors reported that 1) the prevalence of diabetes in Asian populations has increased rapidly in recent decades, 2) in 2007, more than 110 million individuals in Asia were living with diabetes, 3) the "metabolically obese" phenotype (i.e., normal body weight with increased abdominal adiposity) is common in Asian populations (JAMA 301:2129-40, 2009). The adipose tissue overflow hypothesis seemed to be able to explain why South Asians might be so susceptible to central obesity and its atherogenic consequences. According to this hypothesis, as obesity develops, South Asians exhaust the storage capacity of their superficial subcutaneous adipose tissue compartment before white people do, and that is why they develop the metabolic complications of upper body obesity at lower absolute masses of adipose tissue (Intl J Epidemiol 36:220-225, 2007).

In conclusion, Asian populations have restricted accumulation of fat in the subcutaneous adipose tissue while fat accumulation in metabolically less beneficial sites (visceral/liver, etc) is increased. Eastern populations may also have a reduced ability to recruit/differentiate new adipose cells (adipogenesis) in the subcutaneous adipose tissue.

L-6 Characteristics of type 2 diabetes in Japanese

Dr. Ichiro Shimomura

Department of Metabolic Medicine, Osaka University, Osaka, Japan



Dr. Shimomura's group reported the characteristics of type 2 diabetes in Japanese patients in six summaries as follows.

In Japan, after World War II, the prevalence of type 2 diabetes significantly increased, reaching 7.0 % in the whole population in 2007. Especially, in the last 10 years, from 1997 to 2007, the numbers of cases of diabetes suspected diabetes increased 1.6 fold, reaching 22 million, around 17% of the total population.

The increase in diabetes was related to an increase of body weight of Japanese. In males, all the age generations continued to increase their average BMI, and in females, senior generations increased their average BMI. However, most BMIs were less than or equal to 24, while in Caucasian patients with diabetes, average BMI ranges from 28 to 32.

Insulin secretion is more impaired, compared to insulin resistance. In comparison with Caucasian equivalents in the Botnia analysis, Japanese patients with IGT and diabetes were shown to have less insulin resistance and more insufficiency of insulin secretion, especially in the early phase after glucose overload. Deterioration of insulin secretion was overt in Japanese IGT, although insulin secretion was increased in Botnia IGT in a compensatory response to the peripheral insulin resistance.

High insulin secretion is typical in modern overweight patients with IGT/diabetes. In a recent analysis of general population and type 2 diabetes patients, Japanese overweight IGT/diabetes subjects had higher insulin secretion pattern in OGTT, getting closer to that seen in Caucasians, while subjects with less adiposity had a classical lower insulin secretion pattern. However, Japanese overweight patients with diabetes had a deteriorated insulin secretion in the early phase after glucose challenge.

Life style intervention is effective to modern overweight IGT/diabetes. In the Amagasaki city office employees' follow-up, Dr. Shimomura's group showed the health promotion program, "Hokenshido", was effective in overweight Japanese IGT/diabetes, in terms of decreased HbA1c levels correlated with the decrease of BMI and visceral fat amounts.

High fat diet and low physical activity seem to underlie modern type 2 diabetes. Dr. Shimomura's group raised the assumption that a high fat diet and sedentary life style may have caused the increase of type 2 diabetes in modern Japanese. They emphasized the necessity of proper life style intervention to modern slightly overweight Japanese with visceral fat accumulation, to ease the epidemic growth of type 2 diabetes in Japan.

Q & A

Gale: Professor Smith reported that a characteristic of diabetes, or more specifically obesogenic diabetes, is that Japanese subjects have a greater proportion of visceral to subcutaneous fat compared to Europeans. My question to both of you is, if that were the case, why are the Japanese secreting less insulin, because if they are metabolically obese they should be generating the same degree of insulin resistance, and yet I think you've shown us quite clearly that they are secreting less insulin, and are therefore less insulin resistant.

Smith: The issue of differences in insulin secretion is an interesting one that should be pursued? There has just been a very interesting presentation at the JDS regarding differences in postprandial increase in GLP1 between Japanese and Caucasians, and I would like Professor Shimomura to comment on this. The presentation reported that GIP increases but GLP is virtually unchanged. I don't know if this has been verified in other studies, but it is a potentially very interesting finding, possibly contributing to differences in terms of the postprandial insulin response.

Shimomura: We were very interested in GLP1 secretion in terms of the lower insulin secretion shown by Japanese. We compared the insulin GLP1 secretion during OGTT in Japanese non-obese and obese type 2 diabetes, but didn't see any difference between these two groups. Therefore I'm not sure whether adiposity relates to GLP1 secretion in Japanese patients.

Smith: I didn't mean that adiposity would account for this difference, but wondered whether there may be genetic differences in terms of response.?

Shimomura: Indeed, we also saw less GLP1 secretion in Japanese subjects compared to rates reported in Caucasian subjects.

Fujimoto: As a Japanese American, particularly as one who grew up in Hawaii, I'm really happy to see some of this data that has been presented. About 30 years ago we compared diabetic Japanese Americans in Seattle, and diabetic Japanese in Tokyo, and demonstrated that the insulin levels were about 2 to 3 times higher in Japanese American men compared to native Japanese. At that time the average BMI of our Japanese-American men was a little under 25, and in Tokyo it was about 23, so a significant difference. And now you're showing that insulin levels are much higher in Japanese with a BMI of at least 25, and in fact those insulin levels are approaching what we saw in Japanese Americans.

DISCUSSION

Co-chairs Dr. Takashi Kadowaki and Dr. Ulf Smith

Smith: Dr. Kadowaki will chair this first session and then I will chair the second part.

Kadowaki: Are there any questions or comments on any of the talks?

Smith: I think that there are obviously major differences between the typical type 2 Caucasian and Japanese diabetic patients, some of which we touched upon. It looks like the genetic influence as shown by risk genotypes is very similar, although the prevalence or frequency of the risk phenotypes may be different. Therefore would both Dr. Yasuda, and Tim Frayling agree that we really haven't identified any major genetic differences in terms of risk genotypes?

Frayling: Yes, I think that's a fair enough summary. As I said, the risk variants identified so far can often be seen at very different frequencies between East Asians and Europeans, and indeed other populations, but the individual effect of these risk variants seems to be very similar. However there is a bias in coming to that conclusion, because the variants have been identified mainly in Europeans and as Prof. Yasuda noted the Japanese studies are still emerging. We haven't done a good job of finding all of the variants and the variants that we've identified so far only explain a relatively small fraction of the heritable component to diabetes. Therefore it may well be that the variants identified so far are quite homogenous between populations, but the ones we are hoping to identify in the next few years could tell a different story. That is why I commented about a difference between the shifting of the whole population and where an individual is on the scale.

Yasuda: I agree with Professor Frayling. There are several possibilities, firstly, as I mentioned we still have not completed the comprehensive GWAS report in Asia and thus there may be other specific common variants still to be identified in Asian subjects. The second possibility is, as both Professor Frayling and I presented, there may be some rare variants that might be specific to certain phenotypes, or even some subjects. Another possibility is that Japanese have a lower insulin secretory capacity even in the NGT, so there may be differences between the populations themselves. But we cannot identify these types of variants in the studies we have conducted. Thus, while there might be some basic genetic differences between the populations but we are not aware of those kinds of variants.

Kadowaki: I would like to ask a question relating to this issue. The speakers appear to agree that Asian people such as Japanese tend to accumulate visceral rather than subcutaneous fat as compared to Europeans. It was also agreed that insulin secretion capacity is reduced in Asian populations, even though it is not determined yet whether this is due to genetic or environmental influences. Therefore since Dr. Fujimoto proposed that Japanese-Americans develop diabetes at a higher rate, and two major risk factors include visceral adiposity and decreased insulin response to glucose, I would like to ask him what is the general consensus regarding whether visceral adiposity and decreased insulin secretion to glucose are genetically or environmentally determined?

Fujimoto: Yes, in fact, I was going to ask that question of the geneticist. But in Japanese-Americans it looks like visceral fat is the important predictor, and not subcutaneous fat. I know that in some other studies a decrease in subcutaneous fat, in the hip area for example, is related to an increased risk of diabetes.

I tend to agree with you that Asians have a greater propensity to have visceral fat as a risk factor rather than total fat. Since we all think of type 2 diabetes as being polygenic, and certainly in population studies it appears to be a polygenic disease, should we be thinking of type 2 diabetes within an individual as being due to multiple genes, and my second question is, rather than looking at type 2 diabetes as the phenotype, should we not be looking at those intermediate phenotypes that have been strongly linked as risk factors to type 2 diabetes, and the relationship of genes to those? For example, the phenotypes of beta cell function, adiposity, and insulin resistance as risk factors.

Kadowaki: I would like Profs Laakso, Frayling, Shimomura to comment on this.

Frayling: The first question is probably the most important question for the geneticist. That is, is type 2 diabetes a polygenic disease or can we dissect out the heterogeneity and identify genes involved in making the patient beta cell or insulin deficient, and can these genes make the subjects insulin resistant with a slightly different phenotype. At present the answer is that while we've identified the genes, all the variants discussed so far seem to have the same effect on risk, across the range of European diabetic phenotypes, be they lean or obese. Although there may be a slight trend to having stronger effects if you're a lean European diabetic, especially if the effect is principally via beta cell genes. But so far it's looking like there are lots of common variants with small effects, resulting in a sort of normal distribution of diabetes risk.

Fujimoto: The reason I asked this question is because all the genes shown relate to type 2 diabetes, mostly related to beta cells. And we all know that beta cell dysfunction is essential for your type 2 diabetes to develop. You don't need to have obesity, although obesity is an important contributory factor. You don't need insulin resistance, although insulin resistance is a major contributory factor. So I don't think it's surprising that the beta cell allele is reported to be the most strongly linked. Therefore since the other factors contribute, there may be an underlying greater propensity to having a beta cell defect, and the increasing epidemic of obesity and insulin resistance in Asian populations may be bringing this out. I saw a report from Dr. Seino indicating that GLP1 levels might be different between Asian and European populations, relating to activity of DPP4 inhibitor. If that's the case that would explain why glucose stimulated insulin secretion may be less robust in Asian populations.

Kadowaki: My understanding of Prof. Seino's data is that Japanese people may secrete less GLP1 or active GLP1, or alternatively it may be due to differences in the measurement methods.

Smith: But it's a very intriguing finding, it really needs to be clarified.

Laakso: I would like to comment that as Tim said, most of the variants are frequent and you have a combination of variants affecting beta cells, so that's important. Therefore, I feel that the majority of type 2 diabetes are caused by a combination of inherited beta cell defects and acquired insulin resistance. Otherwise the epidemic couldn't be explained, because genes are not changing, but the environment and lifestyle are.

Another issue relates to whether there really are population-specific variants? This doesn't seem to be case for the common variants but data from sequencing the whole genome and exons of known diabetics reveals that there is one rare population-specific variant which is entirely specific to Finns. Therefore it's possible that we can find rare population-specific variants, or mutations, because that was what was found in 1% of Finns. This is an area that needs more research and as more sequencing data becomes available it may clarify the picture.

Kadowaki: Dr. Yasuda and Dr. Shimomura do you have any opinions in response to Dr. Fujimoto's question.

Yasuda: I agree with the possibility of rare variants, but we still don't know exactly what these are like. They may be a structural variant or due to a mutation in the coding region, while others may be even somatic changes. The reason we think most cases of type 2 diabetes are polygenic in origin is because even



in the pedigrees the phenotype might not be identical among subjects. Therefore if the rare variant is the only cause explaining genetic background for the disease, then we should see a very similar phenotype in the pedigrees just like monogenic disease. But that's not always the case. This leads to the belief that there should be several different modes of genetic structure for diabetes susceptibility; some general kind of background factor that is associated with the population difference,

common variants mainly identified by GWAS, and rare variants which may be specific to the sub-phenotype, the pedigree, or even the individual.

Laakso: One of the questions was are there any specific variants for the sub phenotypes such as percentage of waist fat, and BMI ratio, and the answer is yes. All these common variants have not been published yet, but some of the papers are in press. There appears to be trait-specific common variants, at least in Caucasians, but I don't know any results coming from Asians yet.

Mitsuru Ohsugi, The University of Tokyo: With the continuing technological advances we're probably heading to sequencing of the whole genome of healthy subjects or those with type 2 diabetes. What other information do we need? Because the phenotype data we have is sort of like a snapshot, one point patient's BMI, patient's glucose, patients HbA1c, or hopefully some OGTT data. Do we need more data on phenotyping such as more sequential cohort data correlated with the whole genome sequencing? What data is needed to provide necessary insight into genetic environmental interactions.

Frayling: We definitely need more phenotyping data. Most of the genetic variants we have identified are associated with fairly subtle effects, there may be some exceptions with the rare variants, but they are all to a certain extent dependent on how good the phenotyping is. We have overcome this to a certain extent by having larger study numbers, and as ever with any research study, there is a trade-off between depth of phenotyping and sample sizes, and if you can afford to do both, you increase the quality of the phenotyping and the sample size, so much the better. There's always going to be room for more phenotyping.

Laakso: I agree we need more phenotyping data. For example if you try to work out what the HOMA Insulin Resistance Index really means, for me this index doesn't really tell us a great deal, there is an effort now to try and work out the variants associated with sub-populations. For example, I tried to develop tissue-specific indicators for insulin resistance. At the present time phenotyping is too crude, so we definitely should focus on improving this in the future.

Smith: I agree we need detailed phenotyping in order to dissect the potential genetic causes. We've touched on genetics, phenotypes, and insulin secretion, but I would like to move on and ask Dr. Tajima about epidemiology. You mentioned the differences in complications, which we haven't touched on. I understand that end-stage renal disease is a major consequence which is much more predominant in Asian than Caucasian populations and appears earlier. Prof Tajima you mentioned the intensity of screening for microalbuminuria to identify this and lower blood pressure, is this associated with a given phenotype such as higher blood pressure in the Japanese?

Tajima: Japanese patients are more likely to die of end-stage renal disease than Westerners. That's why I think it is important to detect microalbuminuria early as a hallmark of diabetic nephropathy. Some people do progress to diabetic nephropathy early, where hypertension, which is present most of the time, appears to be a major factor in the prediction of its progression. To gain insights into this disease process, we will also need to look at other diabetes phenotypes and complications. Again, we will need to identify genes that are likely to be associated with progression of renal disease.

Smith: Yes this is an important area to investigate and a lot of analysis is ongoing to identify genetic susceptibility profiles, but I was wondering whether is it because the blood pressure is higher and/or that the Asian population is more susceptible to the consequences of a given blood pressure? In the same way that we discussed susceptibility to obesity, and to body fat, is there also an increased susceptibility to high blood pressure?

Tajima: We don't have enough data to answer your question. But we know that if you can keep very strict control of blood pressure, as well as lipids and blood glucose, we are less likely to develop diabetic renal disease, and often we can even see disease regression.

Smith: That is also seen in Caucasians so it is the same. But if we were going to continue investigating this, and for instance really analyzing whether for a given blood pressure complication rates are different between Asian and European subjects, we need prospective data to compare susceptibility between

Japanese/Asians and Europeans. I think that one conclusion from this East-West forum, is that the differences, which can be accounted for by genetic and/or factors that increase the Japanese or the Asian susceptibility to the environment, such as fat, and maybe blood pressure, need to be dissected in greater detail.

Gale: I opened the session by saying one of the aims of the East-West Forum was not just to talk but to devise some experiments. I have a question for the panel, and that is do we have, first of all a clear hypothesis as to what is different phenotypically or environmentally between Japanese and European diabetes. I'm not convinced by the hypothesis that Prof. Smith has put forward, because if he is saying that Japanese diabetes is the same as European, but the metabolic challenge, the visceral adiposity in Japanese is greater, than we are still left with the problem I raised as to insulin secretion. But that is a testable hypothesis. The other thing I'm impressed with is that we talk about genetic elements here but we have seen a 31-fold increase in the genetically stable population over 50 years, there must be something non-genetic going on in this population. So my question to the panel is what is the hypothesis and what is the experiment that needs to be conducted?

Smith: Obviously there is not a simple answer to this, Professor Shimomura, do you want to take on this challenge?

Shimomura: I'm not able to answer that specific question, but regarding the issue of whether Japanese may be more susceptible to accumulating visceral rather than subcutaneous fat, we have recently measured the amount of visceral and subcutaneous fat at the umbilicus by CT in a multicenter, general population based study. Over 5000 Japanese subjects were included. The results demonstrated that Japanese can accumulate subcutaneous fat as well as visceral fat, although it was noted that, particularly in overweight subjects whose BMI was over 25, the amount of accumulated subcutaneous fat did not correlate with the number of metabolic risk factors, although the amount of visceral fat did significantly correlate with the number of metabolic risk factors.

Fujimoto: The principal hypothesis in our Japanese-American study was that there is an underlining genotype in Japanese subjects that makes them susceptible to environmental factors. Therefore I think environmental factors that are responsible for the 31-fold increase may not have been present previously, but the genotype that made them susceptible to those environmental factors has been there for generations. Thus it's incumbent upon geneticists to find out what that genotype is.

Frayling: I was about to say exactly the same thing.

WRAP-UP AND CLOSING REMARKS

Dr. Ulf Smith

I would like to take this opportunity, first of all to thank all the speakers, and of course to Professors Tajima and Gale for helping us organize this, and to the JDS for allowing us to have this joint forum. Speaking on behalf of the EASD, we think that this is a very intriguing, important area, because as we said the major diabetes epidemic is in Asia, not in Europe. We therefore would like to understand what is happening, and would very much like to continue this collaboration with the JDS and to have an East-West Forum in 2011, at the EASD meeting in Lisbon, Portugal. I invite you all to come to next year's meeting. We would also like to enter into a program with the JDS, not only in terms of having a forum and discussion like this, but also to establish scientific collaboration, and to have joint training for European and Japanese scientists in our laboratories.

Finally, we very much look forward to the future, and look at this as the first East West Forum. I think it's been extremely interesting, with a high standard of presentations. I want to thank you all for attending and wish you a safe trip home.

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