Diabetology International (2022) 13:337–343
https://doi.org/10.1007/s13340-022-00570-5

REPORT OF THE COMMITTEE

# New classification and diagnostic criteria for insulin resistance syndrome

**Wataru Ogawa[1] · Eiichi Araki[2] · Yasushi Ishigaki[3] · Yushi Hirota[1] · Hiroshi Maegawa[4] · Toshimasa Yamauchi[5] · Tohru Yorifuji[6] · Hideki Katagiri[7]**

Received: 8 December 2021 / Published online: 31 January 2022


## Abstract

This report of a working group established by the Japan Diabetes Society proposes a new classification and diagnostic criteria for insulin resistance syndrome. Insulin resistance syndrome is defined as a condition characterized by severe attenuation of insulin action due to functional impairment of the insulin receptor or its downstream signaling molecules. This syndrome is classified into two types: genetic insulin resistance syndrome, caused by gene abnormalities, and type B insulin resistance syndrome, caused by autoantibodies to the insulin receptor. Genetic insulin resistance syndrome includes type A insulin resistance as well as Donohue and Rabson-Mendenhall syndromes, all of which are caused by abnormalities of the insulin receptor gene; conditions such as SHORT syndrome caused by abnormalities of *PIK3R1*, which encodes a regulatory subunit of phosphatidylinositol 3-kinase; conditions caused by abnormalities of *AKT2*, *TBC1D4*, or *PRKCE*; and conditions in which a causative gene has not yet been identified. Type B insulin resistance syndrome is characterized by severe impairment of insulin action due to the presence of insulin receptor autoantibodies. Cases in which hypoglycemia alone is induced by autoantibodies that stimulate insulin receptor were not included in Type B insulin resistance syndrome.

**Keywords** Type A insulin resistance syndrome · Type B insulin resistance syndrome · Insulin receptor · Insulin receptor autoantibodies

## Introduction

Insulin resistance syndrome, formerly known as insulin receptor abnormalities, is characterized by pronounced attenuation of insulin action due to functional impairment of insulin receptor signaling [1]. This syndrome has conventionally been classified into type A and type B conditions caused by abnormalities of the insulin receptor gene and by

This article is the English version of the "New classification and diagnostic criteria for insulin resistance syndrome", which was published in J Jpn Diab Soc. 2021;64(11):561-568 in Japanese (https://doi.org/10.11213/tonyobyo.64.561) and has been jointly published in Endocrine Journal (the official English journal of The Japan Endocrine Society: https://doi.org/10.1507/endocrj.EJ21-0725) and Diabetology International (the official English journal of the Japan Diabetes Society).

✉ Wataru Ogawa
ogawa@med.kobe-u.ac.jp

[1] Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

[2] Department of Metabolic Medicine, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honso, Chuo-ku, Kumamoto 860-8556, Japan

[3] Division of Diabetes, Metabolism, and Endocrinology, Department of Internal Medicine, Iwate Medical University, 2-1-1 Idai Street, Shiwagun Yahabacho, Yahaba 028-3695, Japan

[4] Division of Diabetology, Endocrinology, and Nephrology, Department of Medicine, Shiga University of Medical Sciences, Setatsukinowacho, Otsu 520-2192, Japan

[5] Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0003, Japan

[6] Division of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, 2-13-22 Miyakojimahondori, Miyakojima-ku, Osaka 534-0021, Japan

[7] Department of Metabolism and Diabetes, Tohoku University Graduate School of Medicine, 2-1 Seiryomachi, Aoba-ku, Sendai 980-8575, Japan

autoantibodies to the insulin receptor, respectively [2, 3]. The concept of insulin resistance syndrome was first proposed by Kahn et al. in 1976 [1]. The subsequent accumulation of basic and clinical knowledge in Japan by 1990 led to the development of diagnostic criteria for insulin receptor abnormalities type A and type B by the hormone receptor abnormality study group of the Ministry of Health and Welfare, with these criteria being published as a comprehensive study report in 1996 [4]. In this study report, Donohue syndrome and Rabson-Mendenhall syndrome, which are also caused by defects of the insulin receptor gene, were classified as distinct from insulin receptor abnormalities [4].

Although more than 25 years have passed since the publication of this study group report, no revisions have been made to the proposed diagnostic criteria. As a result, certain descriptions, including those of diagnostic tests (such as examination of the number and function of insulin receptors with patient-derived cells), are not consistent with the current clinical situation. Revision of the disease classification and diagnostic criteria has also been needed because of the recent discovery of insulin resistance syndrome triggered by mutations in genes related to signaling downstream of the insulin receptor [5–9]. Moreover, it has become necessary to clarify the classification of individuals with insulin receptor autoantibodies who manifest hypoglycemia but not insulin resistance, possibly as a result of the agonistic nature of the antibodies [10].

The report of a nationwide survey of insulin resistance syndrome conducted by the hormone receptor abnormality study group of the Science Research Grants division (research program on rare and intractable diseases) of the Ministry of Health, Labour, and Welfare (MHLW) was published in 2020 [11]. The accumulation of this clinical information was seen as an opportunity to establish a working group at the Japan Diabetes Society to develop, in cooperation with the MHLW study group, disease classification, and diagnostic criteria for insulin resistance syndrome. The resulting report presented here proposes and explains a new classification and diagnostic criteria for this condition.

## Classification of insulin resistance syndrome (Table 1)

Insulin resistance syndrome has conventionally been classified into type A, caused by abnormalities of the insulin receptor gene (*INSR*), and type B, caused by autoantibodies to the insulin receptor [2, 3]. Although *INSR* abnormalities also give rise to Donohue syndrome and Rabson-Mendenhall syndrome, these conditions were classified as being different from insulin resistance syndrome [4] as a result of the severity of the defects in receptor function and distinctive physical characteristics of affected individuals [12].

**Table 1** Classification of insulin resistance syndrome

| |
|---|
| 1. Genetic insulin resistance syndrome |
| a) *INSR* abnormalities |
| –Type A insulin resistance syndrome |
| –Donohue and Rabson-Mendenhall syndromes |
| b) *PIK3R1* abnormalities (SHORT syndrome) |
| c) Other genetic abnormalities (*AKT2*, *TBC1D4*, *PRKCE*) |
| d) Causative genes not yet identified |
| 2. Type B insulin resistance syndrome |

*PRKCE* genetic abnormalities may be accompanied by clinical symptoms similar to those of SHORT syndrome

However, from a genetic and pathological point of view, it seems appropriate to consider these two syndromes as severe forms of type A insulin resistance syndrome. In general, individuals with type A insulin resistance syndrome harbor a heterozygous abnormality of *INSR*, whereas those with Donohue syndrome or Rabson-Mendenhall syndrome often possess homozygous or compound heterozygous abnormalities [13–15].

Cases of severe insulin resistance triggered by abnormalities of genes related to insulin receptor signal transduction have also been identified. An abnormality of *AKT2* was first identified in such a case [5], with a defect of *TBC1D4*, which encodes a substrate of the protein kinase AKT, subsequently being similarly reported [6]. Given that reports of such cases have been few in number, insulin resistance syndrome due to mutations in such genes appears to be rare.

In 2013, mutations of *PIK3R1* were identified as the cause of SHORT syndrome [7–9]. *PIK3R1* encodes a regulatory subunit (p85α) of phosphatidylinositol 3-kinase, which plays a key role in regulation of the metabolic actions of insulin [16]. SHORT syndrome is so named as a result of the physical features of affected individuals: short stature (S); hyperreflexia/hernia (H); ocular depression (O); Rieger anomaly (R), a malformation of the cornea and iris; and teething delay (T). About half of individuals with SHORT syndrome also develop diabetes mellitus [17]. *PIK3R1* abnormalities have recently been identified in individuals diagnosed with juvenile-onset diabetes with insulin resistance in Japan [18]. It is thus appropriate to classify *PIK3R1* abnormalities as a cause of insulin resistance syndrome. In addition, mutations of the protein kinase C isoform ε gene (*PRKCE*) have been identified in individuals with SHORT syndrome-like physical characteristics as well as insulin resistance [19].

With regard to type B insulin resistance syndrome, instances of amelioration of the syndrome by treatment of comorbid autoimmune disease have been described [20], whereas complete remission as a result of eradication of Helicobacter pylori in a patient with comorbid autoimmune thrombocytopenia was reported [21]. In addition, individuals with autoantibodies to the insulin receptor that manifest

hypoglycemia but not hyperinsulinemia have been identified [10]. Such a condition is likely triggered by autoantibodies that activate insulin receptor function.

On the basis of these various findings, the working group now defines insulin resistance syndrome as a condition characterized by severe attenuation of insulin action as a result of functional impairment of the insulin receptor or of downstream signaling molecules. We also propose that the syndrome be classified into two types: genetic insulin resistance syndrome, including type A insulin resistance syndrome, and type B insulin resistance syndrome.

## Diagnostic criteria for genetic insulin resistance syndrome (Table 2)

Genetic insulin resistance syndrome is often suspected on the basis of low birth weight or other physical characteristics in infancy, whereas it is often diagnosed after the detection of glucose intolerance, such as by a school urine examination, during childhood or adolescence [11]. The key finding for the diagnosis of this condition is the presence of insulin resistance without an apparent cause such as obesity, endocrine disease, chronic inflammatory disease, malignant disease, the use of glucocorticoids or other drugs including antimalignancy agents, and the presence of antibodies to insulin or the insulin receptor. The presence of insulin resistance can be determined on the basis of endogenous hyperinsulinemia, with a fasting serum insulin concentration of > 30 μU/mL being apparent in most Japanese cases of genetic insulin resistance syndrome [11]. Measurement of fasting insulin levels in 89 adult Japanese patients with type 2 diabetes and a body mass index of < 25 kg/m$^2$ revealed no cases with a fasting insulin level of > 30 μU/mL [11]. However, depending on the course of treatment, some cases of genetic insulin resistance syndrome manifest fasting insulin concentrations of < 30 μU/mL [22, 23].

Physical characteristics associated with genetic insulin resistance syndrome include acanthosis nigricans, hypertrichosis, and polycystic ovary, all of which are thought to be triggered by chronic insulin resistance and hyperinsulinemia [2]. Whereas Donohue syndrome and Rabson-Mendenhall syndrome are associated with severe intrauterine growth retardation, type A insulin resistance syndrome and insulin resistance syndrome due to *PIK3R1* abnormalities are often associated with low birth weight. Donohue syndrome and Rabson-Mendenhall syndrome are discriminated from other forms of genetic insulin resistance syndrome on the basis of their associated physical characteristics and comorbid abnormalities such as distinctive facial features, tooth abnormalities, and pineal body abnormalities. However, given that the symptoms

**Table 2** Diagnostic criteria for genetic insulin resistance syndrome

Definition: a condition characterized by severe attenuation of insulin action as a result of insulin signaling defects due to genetic causes

A. Major signs
1. Hyperinsulinemia with no apparent cause of insulin resistance such as obesity or other conditions (fasting serum insulin level of > 30 μU/mL, although this value may depend on the course of treatment for diabetes)

B. Potential reference physical findings or clinical features
1. Juvenile-onset glucose intolerance
2. Acanthosis nigricans
3. Hypertrichosis
4. Polycystic ovary
5. Low birth weight
6. Intrauterine growth retardation, distinctive facial features, loss of subcutaneous fat, deformation of teeth and nails, and pineal hyperplasia in the case of Donohue syndrome and Rabson-Mendenhall syndrome
7. Distinctive facial features and Rieger anomaly in the case of *PIK3R1* abnormalities (SHORT syndrome)

C. Differential diagnosis
1. Lipoatrophic diabetes

D. Genetic testing
1. Abnormalities of the insulin receptor gene (*INSR*) or of genes related to insulin receptor signaling (*PIK3R1*, *AKT2*, *TBC1D4*, *PRKCE*)

E. Diagnostic categories
1. Definite: meeting A, excluding diseases to be differentiated in C, and meeting D
2. Probable: meeting A, excluding diseases to be differentiated in C

F. Severity classification
1. Mild: does not require drug treatment for diabetes despite the presence of insulin resistance
2. Moderate: requires drug treatment for diabetes
3. Severe: requires insulin at ≥ 1 U/kg per day or injection of IGF-1 for treatment of diabetes

If there are no special provisions in the diagnostic criteria, laboratory or clinical findings for any time period may be used for diagnosis. After the initiation of treatment, health care professionals may select the poorest conditions in the previous 6 months under appropriate medical management

of these two syndromes overlap, it is often difficult to differentiate between them. Cases that result in death of newborns or in early childhood mortality are therefore often diagnosed as Donohue syndrome, whereas those that do not result in such early death are often classified as Rabson-Mendenhall syndrome. Donohue syndrome was formerly known as leprechaunism [24], a term that is now considered ethically inappropriate and is no longer used.

About 40 families with *PIK3R1* abnormalities as causes of SHORT syndrome or insulin-resistant diabetes have been reported worldwide [11, 18, 25]. Such genetic abnormalities thus appear to be the second most frequent cause of genetic insulin resistance syndrome, after those affecting *INSR*. In addition to short stature in adulthood, facial features such as a small, protruding jaw, occipital protrusions, and large, low-set auricles are associated with almost all cases of genetic insulin resistance syndrome caused by *PIK3R1* abnormalities, whereas other classical body features of SHORT syndrome are not necessarily observed in these patients [18]. It is important that Silver-Russell syndrome be distinguished from SHORT syndrome, given that it is also characterized by similar facial features, including an inverted triangle–shaped face, a relatively large head, intrauterine growth retardation, and short stature. Mutations in *PIK3R1* also cause immunological defects, with a patient manifesting both the characteristics of SHORT syndrome and an immune disorder having been reported [25].

It is sometimes necessary to differentiate genetic insulin resistance syndrome from lipoatrophic diabetes in the clinical setting, given that the former condition is often also accompanied by a decrease in subcutaneous fat mass, likely as a result of impairment of both insulin-induced triglyceride synthesis and proliferation and differentiation of adipocytes. It has been proposed that genetic insulin resistance syndrome associated with *PIK3R1* abnormalities, in particular, be categorized as a subtype of lipoatrophy [8].

A definite diagnosis of genetic insulin resistance syndrome (diagnostic category: definite) is determined by detection of mutations that likely affect the function of *INSR* or of genes related to insulin receptor signal transduction (including *PIK3R1*, *AKT2*, *TBC1D4*, and *PRKCE*) [26] together with the presence of characteristic clinical features. However, in the nationwide survey of insulin resistance syndrome, cases were identified in which the syndrome was clinically detected but for which mutations in known causative genes were not detected [11]. It is appropriate to tentatively categorize such cases as genetic insulin resistance syndrome with unidentified causative genes. In addition, it is often difficult to perform tests for many candidate genes in the clinical setting. Thus, even if genetic testing is not performed or does not identify a causative gene, individuals suspected of having the syndrome on the basis of endogenous hyperinsulinemia and other clinical manifestations should be categorized as probable genetic insulin resistance syndrome (diagnostic category: Probable).

The clinical manifestations of type A insulin resistance syndrome vary from normal glucose tolerance with hyperinsulinemia to treatment-refractory diabetes even with a large amount of exogenously administered insulin. In addition, reactive hypoglycemia has been found to be caused by type A insulin resistance syndrome [27, 28]. Patients with type A insulin resistance syndrome or with genetic insulin resistance syndrome due to *PIK3R1* abnormalities often develop glucose intolerance after their late teens [1].

Given that metformin and sodium-glucose cotransporter-2 (SGLT-2) inhibitors exert hypoglycemic actions by mechanisms independent of insulin receptor signaling, these drugs are effective in individuals with genetic insulin resistance syndrome. Case reports have thus shown that both metformin and SGLT-2 inhibitors improve glycemic control and allow insulin dose reduction in individuals with this syndrome [29, 30]. In addition to insulin, insulin-like growth factor-1 (IGF-1) is administered to treat Donohue syndrome and Rabson-Mendenhall syndrome [31], although maintenance of good glycemic control in patients with these conditions remains a challenge. Patients with these syndromes often die in infancy or early childhood as a result of infections and other complications of their severe metabolic abnormalities [11, 12].

## Diagnostic criteria for type B insulin resistance syndrome (Table 3)

Type B insulin resistance syndrome is characterized by severe attenuation of insulin action due to autoantibodies to the insulin receptor. The number of individuals newly found to be positive for such autoantibodies in Japan is ~ 22 per year [11], indicating that this syndrome is relatively rare. The presence of insulin resistance can be determined on the basis of endogenous hyperinsulinemia. The fasting insulin concentration is also > 30 μU/mL in many cases of type B insulin resistance syndrome (major sign), with the average level having been found to be 1122.1 ± 3292.5 μU/mL [11]. However, depending on the course of treatment, some individuals with this syndrome manifest a fasting insulin value of < 30 μU/mL. Acanthosis nigricans was observed in 17% of cases in Japan [11] (reference finding). On the other hand, individuals with autoantibodies to the insulin receptor who do not manifest hyperinsulinemia but who develop hypoglycemia as a primary symptom (corresponding to a few percent of people positive for such autoantibodies) do not meet the definition of insulin resistance syndrome and are therefore not categorized as having type B insulin resistance syndrome. A definite diagnosis is made on the basis of the detection of insulin receptor autoantibodies in the presence

**Table 3** Diagnostic criteria for type B insulin resistance syndrome

| Definition: a condition characterized by severe attenuation of insulin action due to autoantibodies to the insulin receptor |
|---|
| A. Major signs |
| 1. Hyperinsulinemia (fasting serum insulin level of > 30 μU/mL, although this value may depend on the course of treatment for diabetes) |
| B. Potential reference physical findings or clinical features |
| 1. Hyperglycemia |
| 2. Hypoglycemia |
| 3. Autoimmune disease (including systemic lupus erythematosus, Sjogren's syndrome, and Hashimoto's disease) or abnormalities on immunological testing |
| C. Other tests |
| 1. Autoantibodies to the insulin receptor |
| D. Diagnostic categories |
| 1. Definite: meeting A and C |

If there are no special provisions in the diagnostic criteria, laboratory or clinical findings for any time period may be used for diagnosis. Some insulin receptor autoantibody-positive cases are accompanied by hypoglycemia as a main symptom and not by hyperinsulinemia. Such cases are not categorized as type B insulin resistance syndrome. Treatment of coexisting autoimmune disease can lead to remission or cure of type B insulin resistance syndrome. Examination of patients for comorbid autoimmune disease is therefore recommended. Acanthosis nigricans may be observed

of hyperinsulinemia. In the nationwide survey of insulin resistance syndrome [11], the ratio of men to women with type B insulin resistance syndrome was 19:11, indicating that it is not necessarily found more often in women, as was stated in the previous diagnostic criteria [4]. The disease was detected most often in people in their 60s, with the average age of onset being $59.6 \pm 16.5$ years [11]. There were no distinct regional differences in prevalence of the disease in Japan.

About 76% of cases of type B insulin resistance syndrome are complicated with hypoglycemia [11], which is thus an important clinical feature together with hyperglycemia. Moreover, among examined individuals with this syndrome, 67% had other autoimmune diseases or abnormalities of immunological test values. The most common associated autoimmune disorder was systemic lupus erythematosus (20%), with others including mixed connective tissue disease, Sjogren's syndrome, autoimmune thyroid disease, autoimmune thrombocytopenia, systemic scleroderma, and rheumatoid arthritis. Given that treatment of comorbid autoimmune disease can result in remission or cure of type B insulin resistance syndrome, examination of patients for such accompanying autoimmune disease is recommended.

## Conclusion

We have formulated disease classification and diagnostic criteria for insulin resistance syndrome on the basis of current knowledge including findings of the recent nationwide survey of insulin resistance syndrome in Japan [11]. The disease classification and diagnostic criteria proposed here should lead to a better understanding of the concept of insulin resistance syndrome as well as facilitate its accurate diagnosis and the selection of appropriate treatments. The Japan Diabetes Society plans to establish a registry of insulin resistance syndrome in collaboration with the MHLW study group. Further revision of the classification and diagnostic criteria for this disease will be necessary in the future on the basis of the additional accumulation of disease information, such as that obtained via the disease registry.

## Declarations

**Conflict of interest** Wataru Ogawa: Lecture fee (Sumitomo Dainippon Pharma Co., Ltd., Novartis Pharma K.K., Nippon Boehringer Ingelheim Co., Ltd., Takeda Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Abbott Japan), Total amount of research expenses (joint research, commissioned research, clinical trials, etc.) and grants (Noster, Nippon Boehringer Ingelheim Co., Ltd., Boehringer Ingelheim Pharma GmbH&Co.KG, Eli Lilly Japan K.K., Novo Nordisk Pharma LTD., Abbott Japan, Abbott Diabetes Care UK Ltd, Sumitomo Dainippon Pharma Co., Ltd.), Total amount of scholarships (incentives) (Kowa Company, Ltd., Novo Nordisk Pharma LTD., Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd., ONO PHARMACEUTICAL CO., LTD., Takeda Pharmaceutical Co. Ltd., Abbott Japan, Novartis Pharma K.K., DAIICHI SANKYO CO., LTD., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Corporation, Nippon Boehringer Ingelheim Co., Ltd.), Eiichi Araki: Lecture fees (AstraZeneca, MSD, ONO PHARMACEUTICAL CO., LTD., Kowa Company, Ltd., Sanofi, DAIICHI SANKYO CO., LTD., Sumitomo Dainippon Pharma Co., Ltd., Novo Nordisk Pharma LTD.) Total amount of scholarships (incentives) (Astellas Pharma Inc., Kowa Company, Ltd., Sanofi, DAIICHI SANKYO CO., LTD., Sumitomo Dainippon Pharma Co., Ltd., Takeda Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., Novo Nordisk Pharma LTD. Bayer Yakuhin Ltd) Endowed chair (ONO PHARMACEUTICAL CO., LTD., Terumo Corporation), Yasushi Ishigaki: Lecture fees (MSD, Novartis Pharma K.K., Mitsubishi Tanabe Pharma Corporation, Sanofi, ONO PHARMACEUTICAL CO., LTD., Sumitomo Dainippon Pharma Co., Ltd., Takeda Pharmaceutical Co. Ltd., Novo Nordisk Pharma LTD.)

Total amount of research expenses (joint research, commissioned research, clinical trials, etc.) and grants (Novo Nordisk Pharma LTD., DAIICHI SANKYO CO., LTD.), Total amount of scholarships (incentives) donations (Novartis Pharma K.K., ONO PHARMACEUTICAL CO., LTD., Takeda Science Foundation), Yushi Hirota: Lecture fee (Eli Lilly Japan K.K. Sanofi), Hiroshi Maegawa: Lecture fees (Sanofi, Nippon Boehringer Ingelheim Co., Ltd., Takeda Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma LTD., Sumitomo Dainippon Pharma Co., Ltd., MSD, Astellas Pharma Inc., DAIICHI SANKYO CO., LTD., AstraZeneca, Eli Lilly Japan K.K.) Total amount of research fees (joint research, commissioned research, clinical trials, etc.) and grants (Nippon Boehringer Ingelheim Co., Ltd., Sunstar, Mitsubishi Tanabe Pharma Corporation, Kyowa Kirin Co., Ltd. And Cimic Co., Ltd., Nissan Chemical Corporation, MIKI Corporation, Parexel), Total amount of scholarships (incentives) (Takeda Pharmaceutical Co. Ltd., Nippon Boehringer Ingelheim Co., Ltd., Mitsubishi Tanabe Pharma Corporation, DAIICHI SANKYO CO., LTD., Sumitomo Dainippon Pharma Co., Ltd., Kowa Company, Ltd., Sanwa Kagakukenkyusho Co, Ltd., Novo Nordisk Pharma LTD., Nipro Corporation, Astellas Pharma Inc., MSD, Taisho Pharma Co., Ltd., ONO PHARMACEUTICAL CO., LTD., Bayer Yakuhin Ltd, Novartis Pharma K.K.), Toshimasa Yamauchi: Lecture fees (Astellas Pharma Inc., AstraZeneca, ONO PHARMACEUTICAL CO., LTD., Sanofi, Takeda Pharmaceutical Co. Ltd., DAIICHI SANKYO CO., LTD., Novartis Pharma K.K., Novo Nordisk Pharma LTD.), Total amount of research expenses (joint research, commission research, clinical trials, etc.) and grants (Astra Zeneca, Kowa Company, Ltd., MSD, DAIICHI SANKYO CO.,LTD., Sanofi, Nippon Boehringer Ingelheim Co.,Ltd., Aero Switch Therapeutics, Inc., Sanwa Kagakukenkyusho Co, Ltd., Minophagen Pharmaceutical Co., LTD., Mitsubishi Corporation Life Sciences Limited, Nipro Corporation), Total amount of scholarships (incentives)(Kissei Pharmaceutical Co., Ltd., Taisho Pharma Co., Ltd., Kowa Company, Ltd., Kyowa Kirin Co., Ltd., Sanofi, Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd., Novo Nordisk Pharma LTD., ONO PHARMACEUTICAL CO., LTD., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co. Ltd., Sanwa Kagakukenkyosho Co, Ltd.), Endowed chair offered by companies, etc. (Takeda Pharmaceutical Co. Ltd., ONO PHARMACEUTICAL CO., LTD., Novo Nordisk Pharma LTD., Mitsubishi Tanabe Pharma Corporation, MSD, Nippon Boehringer Ingelheim Co.,Ltd., Kowa Company, Ltd., NTT Docomo Inc., Asahi Mutual Life Insurance Co), Tohru Yorifuji: Lecture fees (Novo Nordisk Pharma LTD.), Hideki Katagiri: Lecture fees (Mitsubishi Tanabe Pharma Corporation, Sanofi, Novo Nordisk Pharma LTD.), Total amount of research expenses (joint research, commission research, clinical trials, etc.) and grants (Otsuka Pharmaceutical Co., Ltd., Suntory Holdings Limited, Astellas Pharma Inc.), Total amount of scholarships (incentives) donations (Takeda Pharmaceutical Co. Ltd., DAIICHI SANKYO CO., LTD., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Corporation, ONO PHARMACEUTICAL CO., LTD., Eli Lilly Japan K.K., MSD., Sanofi., Novo Nordisk Pharma LTD.)

**Ethical statement** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

1. Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J. The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. N Engl J Med. 1976;294:739–45.
2. Musso C, Cochran E, Moran SA, Skarulis MC, Oral EA, Taylor S, Gorden P. Clinical course of genetic diseases of the insulin receptor (type A and Rabson-Mendenhall syndromes): a 30-year prospective. Medicine (Baltimore). 2004;83:209–22.
3. Arioglu E, Andewelt A, Diabo C, Bell M, Taylor SI, Gorden P. Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance): a 28-year perspective. Medicine (Baltimore). 2002;81:87–100.
4. Araki S, Kasuga M. Insulin receptor abnormalities [type A and type B]. Nihon Rinsho. 1998;56(Suppl 3):579–83 (**In Japanese**).
5. George S, Rochford JJ, Wolfrum C, Gray SL, Schinner S, Wilson JC, Soos MA, Murgatroyd PR, Williams RM, Acerini CL, Dunger DB, Barford D, Umpleby AM, Wareham NJ, Davies HA, Schafer AJ, Stoffel M, O'Rahilly S, Barroso I. A family with severe insulin resistance and diabetes due to a mutation in *AKT2*. Science. 2004;304:1325–8.
6. Dash S, Sano H, Rochford JJ, Semple RK, Yeo G, Hyden CS, Soos MA, Clark J, Rodin A, Langenberg C, Druet C, Fawcett KA, Tung YC, Wareham NJ, Barroso I, Lienhard GE, O'Rahilly S, Savage DB. A truncation mutation in *TBC1D4* in a family with acanthosis nigricans and postprandial hyperinsulinemia. Proc Natl Acad Sci USA. 2009;106:9350–5.
7. Thauvin-Robinet C, Auclair M, Duplomb L, Caron-Debarle M, Avila M, St-Onge J, Le Merrer M, Le Luyer B, Héron D, Mathieu-Dramard M, Bitoun P, Petit JM, Odent S, Amiel J, Picot D, Carmignac V, Thevenon J, Callier P, Laville M, Reznik Y, Fagour C, Nunes ML, Capeau J, Lascols O, Huet F, Faivre L, Vigouroux C, Rivière JB. *PIK3R1* mutations cause syndromic insulin resistance with lipoatrophy. Am J Hum Genet. 2013;93:141–9.
8. Chudasama KK, Winnay J, Johansson S, Claudi T, König R, Haldorsen I, Johansson B, Woo JR, Aarskog D, Sagen JV, Kahn CR, Molven A, Njølstad PR. SHORT syndrome with partial lipodystrophy due to impaired phosphatidylinositol 3 kinase signaling. Am J Hum Genet. 2013;93:150–7.
9. Dyment DA, Smith AC, Alcantara D, Schwartzentruber JA, Basel-Vanagaite L, Curry CJ, Temple IK, Reardon W, Mansour S, Haq MR, Gilbert R, Lehmann OJ, Vanstone MR, Beaulieu CL, FORGE Canada Consortium, Majewski J, Bulman DE, O'Driscoll M, Boycott KM, Innes AM. Mutations in *PIK3R1* cause SHORT syndrome. Am J Hum Genet. 2013;93:158–66.
10. Toshihiro M, Katagiri H, Kataoka K, Fukushima A, Segawa T, Fujiwara T, Hikichi I, Takebe N, Satoh J. Recurrent hypoglycemia during pregnancies in a woman with multiple autoantibodies including anti-insulin receptor antibody and anti-platelet antibody, whose serum lowered murine blood glucose levels and phosphorylated insulin receptor of CHO-IR cells. Endocr J. 2011;58:1037–43.
11. Takeuchi T, Ishigaki Y, Hirota Y, Hasegawa Y, Yorifuji T, Kadowaki H, Akamizu T, Ogawa W, Katagiri H. Clinical characteristics of insulin resistance syndromes: a nationwide survey in Japan. J Diabetes Investig. 2020;11:603–16.
12. Semple RK, Savage DB, Cochran EK, Gorden P, O'Rahilly S. Genetic syndromes of severe insulin resistance. Endocr Rev. 2011;32:498–514.
13. Longo N, Wang Y, Smith SA, Langley SD, DiMeglio LA, Giannella-Neto D. Genotype-phenotype correlation in inherited severe insulin resistance. Hum Mol Genet. 2002;11:1465–75.
14. Kadowaki T, Bevins CL, Cama A, Ojamaa K, Marcus-Samuels B, Kadowaki H, Beitz L, McKeon C, Taylor SI. Two mutant alleles of the insulin receptor gene in a patient with extreme insulin resistance. Science. 1988;240:787–90.
15. Taylor SI. Lilly Lecture: molecular mechanisms of insulin resistance. Lessons from patients with mutations in the insulin-receptor gene. Diabetes. 1992;41:1473–90.
16. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol. 2006;7:85–96.

17. Schwingshandl J, Mache CJ, Rath K, Borkenstein MH. SHORT syndrome and insulin resistance. Am J Med Genet. 1993;47:907–9.
18. Avila M, Dyment DA, Sagen JV, St-Onge J, Moog U, Chung BHY, Mo S, Mansour S, Albanese A, Garcia S, Martin DO, Lopez AA, Claudi T, König R, White SM, Sawyer SL, Bernstein JA, Slattery L, Jobling RK, Yoon G, Curry CJ, Merrer ML, Luyer BL, Héron D, Mathieu-Dramard M, Bitoun P, Odent S, Amiel J, Kuentz P, Thevenon J, Laville M, Reznik Y, Fagour C, Nunes ML, Delesalle D, Manouvrier S, Lascols O, Huet F, Binquet C, Faivre L, Rivière JB, Vigouroux C, Njølstad PR, Innes AM, Thauvin-Robinet C. Clinical reappraisal of SHORT syndrome with *PIK3R1* mutations: toward recommendation for molecular testing and management. Clin Genet. 2016;89:501–6.
19. Alcantara D, Elmslie F, Tetreault M, Bareke E, Hartley T, Care-4Rare Consortium, Majewski J, Boycott K, Innes AM, Dyment DA, O'Driscoll M. SHORT syndrome due to a novel de novo mutation in *PRKCE* (Protein Kinase Cε) impairing TORC2-dependent *AKT* activation. Hum Mol Genet. 2017;26:3713–21.
20. Bloise W, Wajchenberg BL, Moncada VY, Marcus-Samuels B, Taylor SI. Atypical antiinsulin receptor antibodies in a patient with type B insulin resistance and scleroderma. J Clin Endocrinol Metab. 1989;68:227–31.
21. Imai J, Yamada T, Saito T, Ishigaki Y, Hinokio Y, Kotake H, Oka Y, Katagiri H. Eradication of insulin resistance. Lancet. 2009;374:264.
22. Saito-Hakoda A, Nishii A, Uchida T, Kikuchi A, Kanno J, Fujiwara I, Kure S. A follow-up during puberty in a Japanese girl with type A insulin resistance due to a novel mutation in *INSR*. Clin Pediatr Endocrinol. 2018;27:53–7.
23. Harada M, Uchigata Y, Kataoka N, Miura J, Mochizuki H, Yanagisawa K, Sakura H, Iwamoto Y. A case of diabetes mellitus caused by a type A insulin receptor abnormality who has been treated with insulin-like growth actor 1 and oral glycemic agents for 19 years. J Jpn Diabetes Soc. 2010;53:626–30 (**In Japanese**).
24. Donohue WL, Uchida I. Leprechaunism: a euphemism for a rare familial disorder. J Pediatr. 1954;45:505–19.
25. Kushi R, Hirota Y, Ogawa W. Insulin resistance and exaggerated insulin sensitivity triggered by single-gene mutations in the insulin signaling pathway. Diabetol Int. 2020;12:62–7.
26. Petrovski S, Parrott RE, Roberts JL, Huang H, Yang J, Gorentla B, Mousallem T, Wang E, Armstrong M, McHale D, MacIver NJ, Goldstein DB, Zhong XP, Buckley RH. Dominant splice site mutations in *PIK3R1* cause hyper IgM syndrome, lymphadenopathy and short stature. J Clin Immunol. 2016;36:462–71.
27. Ando A, Yatagai T, Rokkaku K, Nagasaka S, Ishikawa S, Ishibashi S. Obesity is a critical risk factor for worsening of glucose tolerance in a family with the mutant insulin receptor. Diabetes Care. 2002;25:1484–5.
28. Højlund K, Hansen T, Lajer M, Henriksen JE, Levin K, Lindholm J, Pedersen O, Beck-Nielsen H. A novel syndrome of autosomal-dominant hyperinsulinaemic hypoglycaemia linked to a mutation in the human insulin receptor gene. Diabetes. 2004;53:1592–8.
29. Hamaguchi T, Hirota Y, Takeuchi T, Nakagawa Y, Matsuoka A, Matsumoto M, Awano H, Iijima K, Cha PC, Satake W, Toda T, Ogawa W. Treatment of a case of severe insulin resistance as a result of a *PIK3R1* mutation with a sodium-glucose cotransporter 2 inhibitor. J Diabetes Investig. 2018;9:1224–7.
30. Nagashima S, Wakabayashi T, Saito N, Takahashi M, Okada K, Ebihara K, Ishibashi S. Long-term efficacy of the sodium-glucose cotransporter 2 inhibitor, ipragliflozin, in a case of type A insulin resistance syndrome. J Diabetes Investig. 2020;11:1363–5.
31. Nakae J, Kato M, Murashita M, Shinohara N, Tajima T, Fujieda K. Long-term effect of recombinant human insulin-like growth factor I on metabolic and growth control in a patient with leprechaunism. J Clin Endocrinol Metab. 1998;83:542–9.