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ORIGINAL ARTICLE

Clinical characteristics of insulin resistance syndromes: A nationwide survey in Japan

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ABSTRACT

Aims/Introduction: Insulin resistance syndrome (IRS) of type A or B is triggered by gene abnormalities of or autoantibodies to the insulin receptor, respectively. Rabson–Mendenhall/Donohue syndrome is also caused by defects of the insulin receptor gene (*INSR*), but is more serious than type A IRS. Here, we carried out a nationwide survey of these syndromes in Japan.

Materials and Methods: We sent questionnaires to a total of 1,957 academic councilors or responsible individuals at certified facilities of the Japan Diabetes Society, as well as at the department pediatrics or neonatology in medical centers with >300 beds.

Results: We received 904 responses with information on 23, 30 and 10 cases of type A or B IRS and Rabson–Mendenhall/Donohue syndrome, respectively. Eight cases with type A IRS-like clinical features, but without an abnormality of *INSR*, were tentatively designated type X IRS, with five of these cases testing positive for *PIK3R1* mutations. Fasting serum insulin levels at diagnosis (mean ± standard deviation) were 132.0 ± 112.4, 1122.1 ± 3292.5, 2895.5 ± 3181.5 and 145.0 ± 141.4 μU/mL for type A IRS, type B IRS, Rabson–Mendenhall/Donohue syndrome and type X IRS, respectively. Type A and type X IRS, as well as Rabson–Mendenhall/Donohue syndrome were associated with low birthweight. Type B IRS was diagnosed most frequently in older individuals, and was often associated with concurrent autoimmune conditions and hypoglycemia.

Conclusions: Information yielded by this first nationwide survey should provide epidemiological insight into these rare conditions and inform better healthcare for affected patients.

INTRODUCTION

Insulin resistance syndromes (IRSs), formerly known as insulin receptor abnormalities, are characterized by insulin resistance as a result of dysfunction of the insulin receptor[1]. These syndromes have classically been categorized as type A or type B, in which insulin receptor function is impaired as a result of mutations in the receptor gene (*INSR*) or the presence of autoantibodies to the receptor, respectively[2,3]. Rabson–Mendenhall syndrome and Donohue syndrome are also caused by abnormalities of *INSR*, but these syndromes are characterized by more serious symptoms resulting from profound defects in receptor function[4].

In type B IRS, autoantibodies block insulin binding to its receptor and thereby cause insulin resistance, whereas some patients with type B IRS paradoxically manifest episodic hypoglycemia[5]. This syndrome is often accompanied by a variety of autoimmune conditions[5–7]. There is no established therapy for type B IRS, although immunological interventions – such as the administration of immunosuppressive drugs[8] or immunoglobulin[9] or the performance of plasmapheresis[10] – have been found to be effective in some, but not all,[2,11] cases. In addition, a case of type B IRS accompanied by idiopathic thrombocytopenic purpura (ITP) was reported in which eradication of *Helicobacter*

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pylori for treatment of ITP cured not only ITP, but also the IRS[12].

Whereas a number of case reports and some case series have been published[2,3,13], information relating to epidemiological surveillance of IRSs has not been available. Furthermore, clinical features similar to those of type A IRS (such as early disease onset, as well as persistent and severe insulin resistance without apparent humoral or metabolic causes) have also been reported for individuals who do not harbor *INSR* defects. Whereas some of these conditions are likely attributable to genetic abnormalities of postreceptor signaling[14,15], data for such patients are limited. Information, such as disease prevalence, sex differences, peak age at onset, proportions of patients with hypoglycemia or autoimmune disease and the effectiveness of therapy (in particular, eradication of *H. pylori*), is lacking for type B IRS.

To provide insight into the characteristics of IRSs, we carried out a nationwide survey for type A IRS, type B IRS, Rabson–Mendenhall syndrome and Donohue syndrome in Japan. We also collected information on patients with type A IRS-like features, but without a mutation in *INSR*, a condition that we here term type X IRS.

METHODS

Collection of information

This study was approved by the ethics committees of Iwate Medical University (approval no. H28-40) and Kobe University Graduate School of Medicine (approval no. 160116), and carried out in accordance with the Declaration of Helsinki and its amendments. In November 2014, we sent a questionnaire to a total of 1,063 academic councilors or responsible individuals at certified facilities of Board Certified Diabetologists of the Japan Diabetes Society. The questionnaire asked whether they had undertaken care of patients with type A IRS, type B IRS, Rabson–Mendenhall syndrome or Donohue syndrome between October 2008 and December 2014. We then sent a second questionnaire in January 2016 to the facilities that had undertaken such patient care during the specified period to collect detailed information. We also sent a questionnaire in October 2016 to a total of 894 responsible individuals at the department of pediatrics or neonatology in medical centers with >300 beds in Japan. In this latter questionnaire, we asked whether the pediatricians had experienced care of patients with the syndromes between October 2008 and December 2014, and, if they had, to answer questions relating to the characteristics of the patients.

Definition of syndromes

A confirmed case of type A IRS was defined by the presence of insulin resistance without an apparent humoral or metabolic cause in an individual harboring a mutation of *INSR*. A suspected case of type A IRS was defined by suspicion based on clinical and laboratory findings in an individual who did not undergo genetic testing. Confirmed cases of Rabson–Mendenhall syndrome or Donohue syndrome were defined by the presence of insulin resistance without an apparent humoral or metabolic cause in early infancy in an individual harboring a mutation of *INSR*. Suspected cases of these two syndromes were defined by suspicion based on clinical and laboratory findings in an individual who did not undergo genetic testing. Given that the difference between Rabson–Mendenhall syndrome and Donohue syndrome is unclear[16,17], we combined information on these syndromes and considered them together as Rabson–Mendenhall/Donohue syndrome in our analysis. We defined type B IRS as the presence of hyperglycemia or hypoglycemia (or both) in individuals positive for autoantibodies to the insulin receptor.

We also collected information on patients who were suspected of having type A IRS or Rabson–Mendenhall/Donohue syndrome on the basis of clinical and laboratory findings, but who had undergone genetic testing that showed no abnormality of *INSR*. This condition was here designated type X IRS. Lipodystrophy or lipodystrophic diabetes, diagnosed either by genetic testing or on the basis of clinical manifestations, was excluded from the survey.

Genetic testing

We sequenced all 22 exons of *INSR* for suspected cases of type A IRS and of Rabson–Mendenhall/Donohue syndrome and all 16 exons of *PIK3R1* for patients categorized as having type X IRS if they and their attending physicians desired it.

RESULTS

Number of participants with each type of IRS

We sent a total of 1,957 questionnaires and received 904 responses. We obtained information on 17 and nine confirmed and suspected cases of type A IRS, respectively, eight and two confirmed and suspected cases of Rabson–Mendenhall/Donohue syndrome, respectively, five cases of type X IRS, and 30 cases of type B IRS (Figure 1).

We sequenced *INSR* for one and five suspected cases of Rabson–Mendenhall/Donohue syndrome and type A IRS, respectively, and found mutations in one and two cases, respectively, which were then re-categorized as confirmed cases. The three suspected cases of type A IRS that tested negative for a mutation of *INSR* were re-categorized as type X IRS (Figure 1). After *INSR* sequencing, the numbers of confirmed and suspected cases of type A IRS were thus 19 and four, respectively, and those of confirmed and suspected cases of Rabson–Mendenhall/Donohue syndrome were nine and one, respectively (Figure 1).

After we received the questionnaire responses, three patients with type X IRS were shown to harbor mutations in *PIK3R1*, which encodes a regulatory subunit of phosphoinositide 3-kinase (PI 3-kinase)[18–20], as a result of analysis carried out independently of the present study[21,22]. We sequenced *PIK3R1*

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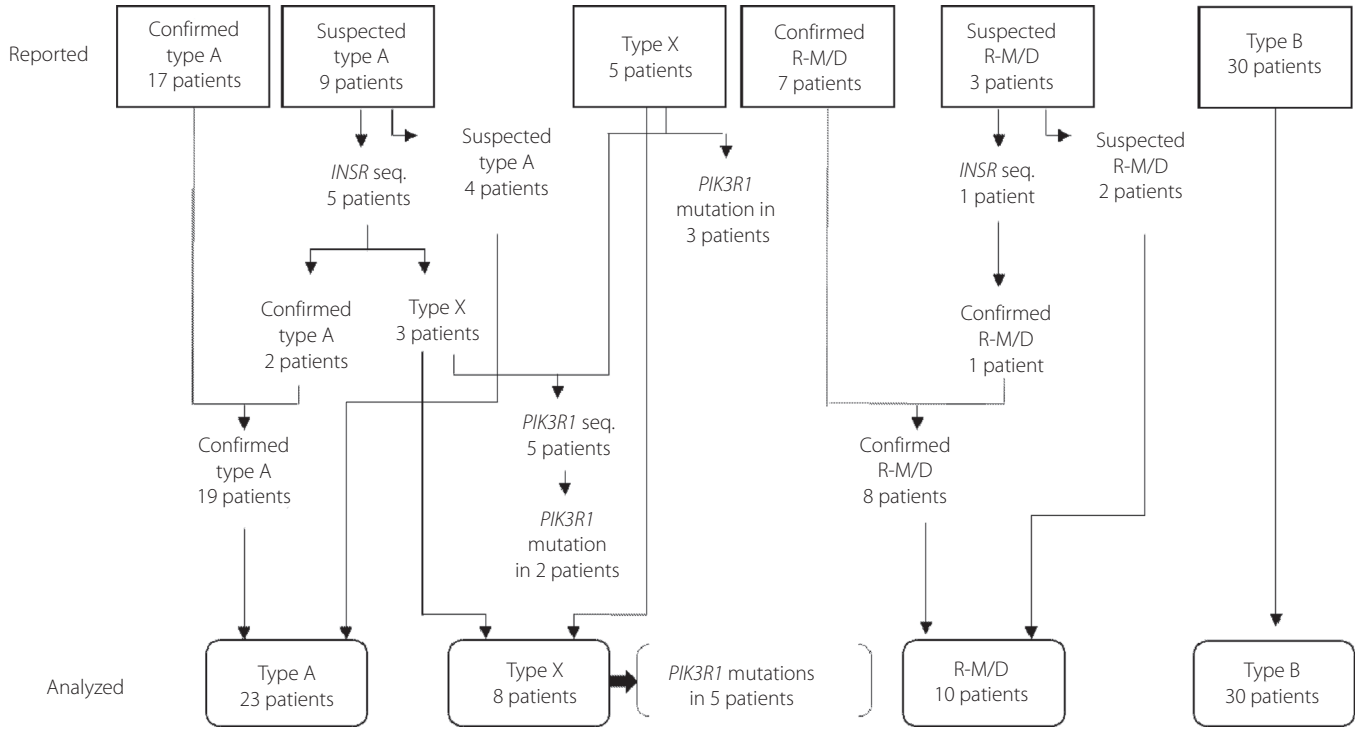

Figure 1 | Numbers of patients with type A, type X or type B insulin resistance syndrome and of Rabson–Mendenhall/Donohue (R-M/D) syndrome. The numbers of patients reported in the questionnaires (upper) and those after re-categorization on the basis of gene sequencing (lower) are shown.

in the remaining five patients with type X IRS, and detected *PIK3R1* mutations in two patients. Among the eight patients with type X IRS, five patients were thus found to be positive for mutations in *PIK3R1* (Figure 1).

Characteristics of type A IRS

Information for 23 patients (4 males, 19 females) with type A IRS, including 19 confirmed and four suspected cases, is presented in Table 1. Age and hemoglobin A_{1c} (HbA_{1c}) level at the time of clinical diagnosis (mean ± standard deviation) were 17.6 ± 13.8 years (range 0–66 years) and 8.0 ± 2.6% (range 5.2–14.9%), respectively. The fasting serum insulin concentration at the time of clinical diagnosis and birthweight for these patients are shown in Figure 2. Treatment for diabetes included insulin (8 patients, 35%), recombinant human insulin-like growth factor-1 (2 patients, 9%), metformin (13 patients, 57%), a sodium–glucose cotransporter (SGLT)-2 inhibitor (4 patients, 17%), a dipeptidyl peptidase-4 inhibitor (3 patients, 13%), an α-glucosidase inhibitor (2 patients, 9%), a sulfonylurea (1 patient, 4%) and diet alone (2 patients, 9%), and the HbA_{1c} level at the time of the survey was 8.1 ± 2.9% (range 4.8–14.9%; Table 1).

Among the 19 confirmed cases, 16, one and two cases harbored a single heterozygous, a single homozygous and multiple heterozygous mutations, respectively, in *INSR* (Table 1). The *INSR* mutations identified in two patients (patients 14 and 18) were previously detected in patients with type A IRS[23,24].

Characteristics of Rabson–Mendenhall/Donohue syndrome

Information for 10 patients (5 males, 5 females) with Rabson–Mendenhall/Donohue syndrome, including eight confirmed and two suspected cases, is shown in Table 2. All the patients were clinically diagnosed before 1 year-of-age. The fasting serum insulin concentration at the time of clinical diagnosis and birthweight are shown in Figure 2. Four patients had died by the time of the survey, with their age at death being 3 months for two patients, 17 months for one patient and 3 years for one patient. Treatment for diabetes included insulin (10 patients, 100%), recombinant human insulin-like growth factor-1 (9 patients, 90%), metformin (6 patients, 60%), an SGLT-2 inhibitor (1 patient, 10%), an α-glucosidase inhibitor (3 patients, 30%) and a dipeptidyl peptidase-4 inhibitor (2 patients, 20%), and the HbA_{1c} level at the time of the survey was 8.7 ± 3.0% (3.6–12.5%; Table 2).

Among the eight confirmed patients, one, one and six patients harbored a single heterozygous, a single homozygous and multiple heterozygous mutations, respectively, in *INSR* (Table 2). The *INSR* mutation identified in one patient in the present study (patient 8) had not previously been described in a patient with either type A IRS or Rabson–Mendenhall/Donohue syndrome.

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Table 1 | Clinical information for patients with type A insulin resistance syndrome

Patient	Age at diagnosis (years)/sex	Fasting serum insulin at diagnosis (μU/mL)	HbA_{1c} at diagnosis (%)	Birthweight (g)	Age at survey (years)	BMI at survey (kg/m^2)	HbA_{1c} at survey (%)	Therapy for diabetes at survey	*INSR* mutation
1[43]	11/M	71.9	6.1	2,392	16	27.8	5.6	Metformin	Gly1146Arg heterozygous
2[44]	9/F	44.1	6.6	1,894	12	21.8	5.1	Metformin	Gln205Ter heterozygous
3	13/F	59.9	5.3	NA	16	18.4	4.8	Metformin	Gly1035Val heterozygous
4	11/F	NA	9.2	1,926	11	17.4	5.8	Metformin	Arg1201Trp heterozygous
5[45]	11/F	65.7	6.9	2,495	21	NA	6.9	Metformin	Arg331Ter heterozygous
6	12/F	279.3	8.8	2,090	16	19.3	9.3	Insulin (CSII, 58 U), metformin, α-GI, DPP-4i, SGLT-2i	Asn489Asp heterozygous, Val1054Met heterozygous
7[46]	10/F	389	8.1	1,511	13	19.8	12.2	Metformin, rhIGF-1	Ser835Ile heterozygous, Ala842Val heterozygous
8[47]	13/F	234	NA	NA	43	20.5	8.4	Bolus insulin	Arg252His homozygous
9	35/F	88.6	7.1	NA	42	22.9	8.0	Basal insulin	Arg120Gln heterozygous
10	35/F	169.1	9.9	NA	46	21.1	10.0	SGLT-2i	Arg120Gln heterozygous
11[48]	0/F	199	5.6	NA	34	19.1	6.2	Metformin	Asn462Ser heterozygous
12[45]	66/F	30.2	7.8	NA	77	19.7	7.7	Metformin, SU, DPP-4i	Arg331Ter heterozygous
13	20/F	168	13.8	NA	35	21.5	13.8	Basal insulin (18 U)	Leu1199Phe heterozygous
14	17/F	105	7.2	NA	25	21.9	7.2	Metformin, bolus insulin (15 U)	Pro1205Leu heterozygous
15[49]	32/F	68.8	7.5	NA	40	22.7	7.5	Metformin, SGLT-2i, α-GI, basal (30 U) and bolus (78 U) insulin	Leu999del heterozygous
16[49]	16/F	61	5.8	NA	49	18.7	5.8	Diet	Leu999del heterozygous
17[50]	14/F	55	8.3	NA	47	19.1	8.3	Bolus insulin (26 U)	Ala145Val heterozygous
18	12/F	61.1	5.2	NA	31	22.5	5.2	Metformin	Arg1201Gln heterozygous
19[49]	27/M	NA	10.5	NA	51	24.8	10.5	NA	Leu999del heterozygous
20	9/M	404	NA	NA	16	18.8	4.8	Diet	ND
21	7/M	150	14.9	1,950	43	15.9	14.9	Basal (40 U) and bolus (120 U) insulin	ND
22	14/F	35	8.1	NA	25	32.3	11.3	DPP-4i, SGLT-2i	ND
23[51]	10/F	21.1	5.7	NA	37	16.5	7.2	Metformin, rhIGF-1	ND

α-GI, α-glucosidase inhibitor; BMI, body mass index; F, female; HbA_{1c}, hemoglobin A_{1c}; DPP-4i, dipeptidyl peptidase-4 inhibitor; M, male; NA, information not available; ND, not determined; SGLT-2i, sodium–glucose cotransporter-2 inhibitor; rhIGF-1, recombinant human insulin-like growth factor–1; SU, sulfonylurea.

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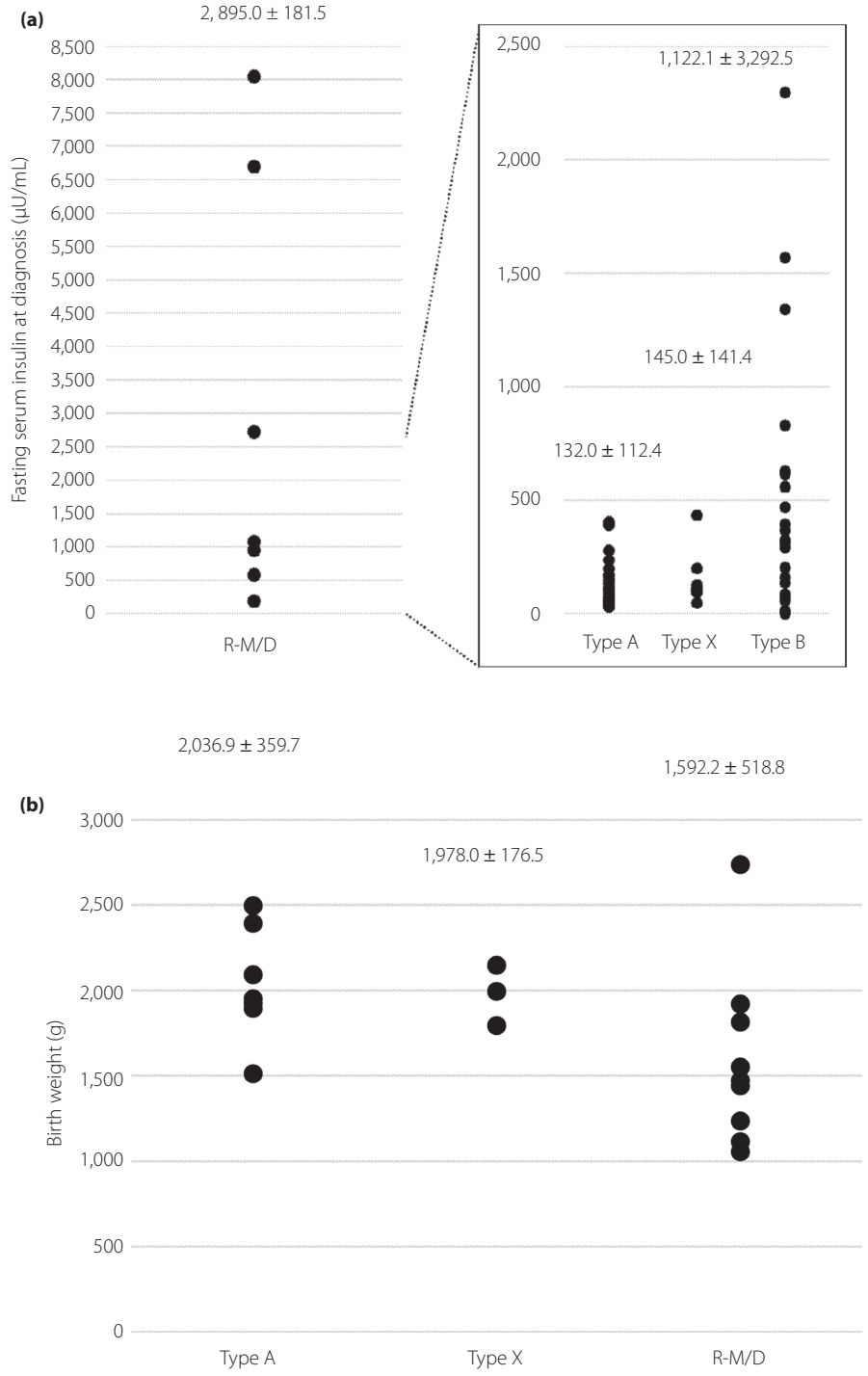

Figure 2 | Fasting serum insulin level at (a) clinical diagnosis and (b) birth weight for cases of type A, type X, or type B insulin resistance syndrome and of Rabson–Mendenhall/Donohue (R-M/D) syndrome. Mean ± standard deviation values are shown.

Characteristics of type X IRS

Information for eight patients (3 males, 5 females) with type X IRS is shown in Table 3. Age and HbA_{1c} level at the time of clinical diagnosis were 13.4 ± 1.7 years and 7.8 ± 0.8%, respectively. The fasting serum insulin concentration at the time of clinical diagnosis and birthweight are shown in Figure 2. Treatment for diabetes included insulin (1 patient, 13%), metformin (5 patients, 63%), an SGLT-2 inhibitor (1 patients, 13%), an α-glucosidase inhibitor (2 patients, 25%), a thiazolidinedione (1 patient, 13%) and diet alone (3 patients, 38%), and the HbA_{1c}

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Table 2 | Clinical information for patients with Rabson–Mendenhall/Donohue syndrome

Patient	Age at diagnosis (years)/sex	Fasting serum insulin at diagnosis (μU/mL)	HbA_{1c} at diagnosis (%)	Birthweight (g)	Age at survey (years)	BMI at survey (kg/m^2)	HbA_{1c} at survey (%)	Therapy for diabetes at survey	*INSR* mutation
1[52]	0/M	8,038	2.8	1,440	7	14.3	10.3	Metformin, basal insulin, rhIGF-1	Thr937Met heterozygous, Ala1204Thr heterozygous
2[43]	0/F	1,070	7.1	1,234	Died at 17 months	NA	3.6	Insulin, rhIGF-1	Ser98Arg homozygous
3	0/M	NA	NA	1,470	Died at 3 years	NA	NA	Insulin, rhIGF-1	Val657Phe heterozygous, deletion including exon 2† heterozygous
4[53]	0/F	NA	6.5	2,736	26	20.3	8.1	Metformin, α-GI, DPP-4i, insulin, rhIGF-1	Met910Thr heterozygous, 1-bp deletion in exon 19† heterozygous
5	0/M	586.8	NA	1,814	18	21.2	NA	Metformin, α-GI, DPP-4i SGLT-2i, basal insulin (70 U), rhIGF-1	Cys981Asp heterozygous, Cys1126Asp heterozygous, Phe1144Ser heterozygous
6[54]	0/M	6,702	NA	1,920	6	17.5	10.0	Insulin, metformin, rhIGF-1	Thr910Met heterozygous, Glu1047Lys heterozygous
7[55]	0/F	185	6.6	1,550	27	15.3	12.5	Metformin, α-GI, basal (240 U) and bolus (240 U) insulin	Arg1201Trp heterozygous, deletion including exons 4–6† heterozygous
8	0/F	2,730	5.8	NA	10	14.9	7.6	Insulin, metformin, rhIGF-1	Ile925Ser heterozygous
9[56]	0/F	956.4	23	1,054	Died at 3 months	10.3	NA	Insulin, rhIGF-1	ND
10	0/M	NA	NA	1,112	Died at 3 months	NA	NA	Insulin, rhIGF-1	ND

α-GI, α-glucosidase inhibitor; BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; F, female; HbA_{1c}, hemoglobin A_{1c}; M, male; NA, information not available; ND, not determined; rhIGF-1, recombinant human insulin-like growth factor-1; SGLT-2i, sodium–glucose cotransporter-2 inhibitor. †Detailed information not available.

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Table 3 | Clinical information for patients with type X insulin resistance syndrome

Patient	Age at diagnosis (years)/sex	Fasting serum insulin at diagnosis (μU/mL)	HbA_{1c} at diagnosis (%)	Birthweight (g)	Age at survey (years)	BMI at survey (kg/m^2)	HbA_{1c} at survey (%)	Therapy for diabetes at survey	Mutation
1	13/F	199	7.4	NA	15	25.0	7.4	Diet	ND
2	15/M	46.1	6.8	1,994	16	13.0	7.3	Metformin	*PIK3R1* Arg649Trp heterozygous
3	12/F	104.4	7.4	NA	17	19.6	6.2	Metformin, α-GI	ND
4	14/M	92.5	7.2	2,146	20	16.7	6.7	Metformin, α-GI	*PIK3R1*[†]
5[21]	NA/M	NA	NA	1,794	2	12.5	NA	None	*PIK3R1* Arg649Trp heterozygous
6	11/F	NA	8.9	NA	19	21.1	5.7	Diet	ND
7	13/F	433.8	8.8	NA	20	23.9	6.9	Metformin, thiazolidinedione	*PIK3R1* Arg649Trp heterozygous
8[21]	16/F	128	8.0	NA	38	19.3	7.6	Metformin, SGLT-2i, insulin (80U)	*PIK3R1* Arg649Trp heterozygous

α-GI, α-glucosidase inhibitor; BMI, body mass index; F, female; HbA_{1c}, hemoglobin A_{1c}; M, male; NA, information not available; ND, not determined; SGLT-2i, sodium–glucose cotransporter-2 inhibitor. [†]Detailed information not available.

level at the time of the survey was 6.8 ± 0.7% (range 5.7–7.6%; Table 3).

Five patients were found to harbor mutations in *PIK3R1*. Mutations of this gene are responsible for SHORT (Short stature, Hyperextensibility of joints and/or inguinal hernia, Ocular depression, Rieger anomaly, and Teething delay) syndrome[18–20,25,26], and four of the five patients who where type X IRS-positive for such mutations harbored Arg649Trp (Table 3), one of the most frequent mutations previously described in SHORT syndrome[27]. These four patients, including a mother and son (patients 5 and 8), manifested a recognizable facial gestalt (including a triangular face, prominent forehead, small chin and ocular depression) that is characteristic of SHORT syndrome. Other bodily characteristics of SHORT syndrome, including hyperextensibility of joints, inguinal hernia and Rieger anomaly[27,28], were not apparent in these patients. The height of the four adult patients with *PIK3R1* mutations was 158.5 ± 13.3 cm.

Characteristics of type B IRS

Information for 30 patients (19 males, 11 females) with type B IRS is shown in Table 4. The age and HbA_{1c} level at the time of clinical diagnosis were 59.6 ± 16.5 years (range 13–85 years) and 8.2 ± 2.5% (range 4.3–14.1%), respectively. The age at diagnosis showed a peak in the 60s (Figure 3a). The fasting serum insulin concentration at the time of clinical diagnosis is shown in Figure 2a. A total of 18 patients had experienced episodic hypoglycemia (Figure 3b), and 17 patients were accompanied by confirmed autoimmune conditions, including SLE, Sjögren's syndrome, Hashimoto's disease, mixed connective tissue disease, Graves' disease, ITP, scleroderma and rheumatoid arthritis (Table 5).

A total of 14 patients received immunomodulation therapy, including glucocorticoid, immune suppressant or immunoglobulin administration, as well as eradication of *H. pylori* (Table 6). Treatment for diabetes included insulin (14 patients, 47%), metformin (8 patients, 27%), recombinant human insulin-like growth factor-1 (4 patients, 13%), a glucagon-like peptide-1 receptor agonist (4 patients, 13%), a dipeptidyl peptidase-4 inhibitor (6 patients, 20%), an α-glucosidase inhibitor (8 patients, 27%), a thiazolidinedione (4 patients, 13%), a sulfonylurea (3 patients, 10%), a glinide (2 patients, 7%) and an SGLT-2 inhibitor (1 patient, 3%), and the HbA_{1c} level at the time of the survey was 6.5 ± 1.4% (range 4.8–10.6%).

Physical findings

Acanthosis nigricans and hirsutism were commonly observed in patients with type A IRS or Rabson–Mendenhall/Donohue syndrome, but were relatively uncommon with type B IRS (Table 7). Scarce fat tissue was apparent more frequently in Rabson–Mendenhall/Donohue syndrome than in the other syndromes. Characteristic facial appearance was also common in Rabson–Mendenhall/Donohue syndrome. All patients with

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Table 4 | Clinical information for patients with type B insulin resistance syndrome

Patient	Age at diagnosis (years)/ sex	Fasting serum insulin at diagnosis (μU/mL)	BMI at diagnosis (kg/m^2)	HbA_{1c} at diagnosis (%)	Concurrent autoimmune disease	Immunomodulating therapy	Therapy for diabetes	Hypoglycemia
1	13/F	395	19.5	14.1	SLE	mPSL, azathioprine	Insulin (180 U)	–
2[57]	45/F	73.6	18.0	10.8	MCTD		Insulin (525 U), liraglutide	+
3[58]	69/F	324.6	19.1	9.8	NI	Eradication of *Helicobacter pylori*	SU, DPP-4i, α-GI, metformin, SGLT-2i	–
4	68/M	ND	20.0	ND	MCTD		ND	+
5[59]	56/M	ND	22.7	ND	NI		ND	+
6[60]	65/M	310	21.4	7.9	NI	PSL (12.5 mg/day)	α-GI, metformin	+
7	62/M	627.4	18.5	4.9	NI		Insulin (18 U), liraglutide	–
8[61]	60/M	620.4	20.0	13.0	SLE Hashimoto's disease	Cyclosporine (25 mg), PSL (10 mg)	Insulin (100 U), metformin	–
9	52/F	617.7	14.6	8.0	RA		Thiazolidinedione, metformin, bolus insulin (65 U)	+
10	17/F	12.1	20.8	5.1	SLE	PSL (17.5 mg)	DPP-4i, glinide	+
11	69/M	292.4	23.2	8.3	NI		Insulin (64 U)	+
12	61/F	620	27.6	8.7	SLE, SJS, Hashimoto's disease		Insulin (34 U)	–
13	72/F	615	21.2	11.1	SJS		rhIGF-1, α-GI	+
14[62]	32/F	0.5	22.4	4.3	ITP	Hydrocortisone (15 mg/day), human immunoglobulin (27.5 g/day)		+
15	69/M	493	23.5	5.5	NI	PSL		–
16[12]	84/M	138	37.4	9.0	ITP	Eradication of *H. pylori*		–
17	61/F	560	19.8	12.1	SJS, Hashimoto's disease	PSL	Insulin, rhIGF-1	–
18	67/M	88	16.4	5.7	Graves' disease	Eradication of *H. pylori*, PSL (50 mg)		+
19	85/M	1,568	26.4	6.4	NI	PSL (25 mg)		+
20	72/M	2,294	18.0	8.3	SJS		Insulin (8 U), liraglutide, thiazolidinedione, DPP-4i, α-GI	+
21	42/M	13.3	27.8	5.8	NI		SU, DPP-4i, metformin	–
22[63]	59/M	316	15.6	9.5	SLE	PSL (30 mg)	Insulin (610 U), rhIGF-1	+
23[63]	50/F	830	23.3	8.0	SLE	Cyclosporine (250 mg), PSL (30 mg)	Insulin (68 U), rhIGF-1, metformin, thiazolidinedione	+
24	75/F	202	24.0	8.4	Graves' disease		Insulin (60 U), thiazolidinedione, SU	–
25	65/M	1,7390	ND	6.5	NI		Insulin (20 U), DPP-4i, metformin,	+
26	67/M	471.1	27.7	9.1	NI		Insulin (30 U), DPP-4i, metformin	+

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Table 4 (*Continued*)

Patient	Age at diagnosis (years)/ sex	Fasting serum insulin at diagnosis (μU/mL)	BMI at diagnosis (kg/m^2)	HbA_{1c} at diagnosis (%)	Concurrent autoimmune disease	Immunomodulating therapy	Therapy for diabetes	Hypoglycemia
27[64]	70/M	366	21.1	8.6	NI		α-GI	+
28	68/M	1,340	29.0	7.2	NI	PSL (20 mg/day)	Glinide, α-GI	–
29	41/M	10	37.4	4.7	NI		α-GI	–
30	54/M	158	17.0	9.6	Scleroderma		Liraglutide, α-GI	+

ssssα-GI, α-glucosidase inhibitor; BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; F, female; HbA_{1c}, hemoglobin A_{1c}; ITP, idiopathic thrombocytopenic purpura; M, male; MCTD, mixed connective tissue disease; mPSL, methylprednisolone; NI, not identified; PSL, prednisolone; RA, rheumatoid arthritis; rhIGF-1, recombinant human insulin-like growth factor-1; SLE, systemic lupus erythematosus; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SJS, Sjögren's syndrome; SU, sulfonylurea.

type X IRS who manifested the characteristic facial appearance harbored mutations in *PIK3R1*.

Triggers for diagnosis

Low birthweight and urinalysis abnormalities at school were the most frequent triggers for diagnosis of Rabson–Mendenhall/Donohue syndrome or of type A or type X IRS, respectively (Table 8). Whereas type B IRS was diagnosed most frequently by recognition of hyperglycemia, hypoglycemia triggered the diagnosis of this syndrome in some patients.

DISCUSSION

We carried out a nationwide survey of type A and type B IRS, as well as Rabson–Mendenhall/Donohue syndrome in Japan. As far as we are aware, this is the first such nationwide epidemiological survey for these syndromes in any country.

We sent questionnaires to healthcare professionals who treat mostly adult or non-adult patients, thereby likely covering most of the institutions that provide care for these rare diseases in Japan. In Japan, only one clinical testing company undertakes testing for autoantibodies to the insulin receptor. An enquiry to the company revealed that they had tested samples from 1,796 individuals, and that 88 of these samples had tested positive between April 2009 and March 2013. Whereas these individuals included those who had already been diagnosed with type B IRS before April 2009, it is likely that approximately 20 cases of this syndrome are diagnosed per year in Japan. Given that we collected information on 30 patients with this syndrome who had received care during an approximately 6-year period, our survey likely covered about one-quarter of such patients nationwide.

Among patients for whom information on *INSR* mutations was available, 84.2% (16/19) of type A IRS patients harbored a single heterozygous mutation, whereas 87.5% (7/8) of Rabson–Mendenhall/Donohue syndrome patients harbored either a homozygous or multiple heterozygous mutations, consistent with the notion that the more serious nature of Rabson–Mendenhall/Donohue syndrome is due to defects in both *INSR* alleles[29,30]. Given that 10 patients were found to harbor *INSR* mutations in both alleles (3 with type A IRS and 7 with Rabson–Mendenhall/Donohue syndrome) and that the population of Japan is approximately 126 million, at least 0.05% of the population might harbor a pathological *INSR* mutation in one allele according to a calculation based on the Hardy–Weinberg principle: $2 \times (10 / 126{,}000{,}000)^{1/2} \times 100 \approx 0.05$. Given that the coverage of our survey was not 100%, it is likely that the proportion of the population harboring such mutations is actually >0.05%. It is likely that most individuals who harbor a mutation of *INSR* in one allele manifest minimal metabolic disturbance and remain unidentified. A recent study found that, among individuals who underwent a health checkup, 0.4% (33/8630) showed hyperinsulinemia (>15 μU/mL during fasting) without obesity (body mass index of <25 kg/m^2), and that two of the 11 such individuals tested harbored a single heterozygous *INSR* mutation[31].

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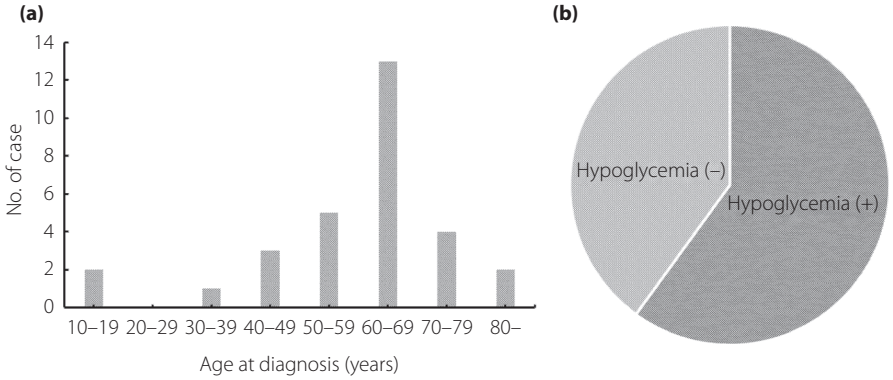

Figure 3 | Prevalence of (a) age at diagnosis and (b) hypoglycemia for cases of type B insulin resistance syndrome.

Table 5 | Concomitant autoimmune diseases for patients with type B insulin resistance syndrome

Autoimmune disease	No. patients
Systemic lupus erythematosus	6 (20.0%)
Mixed connective tissue disease	2 (6.7%)
Sjögren's syndrome	4 (13.3%)
Hashimoto's or Graves' disease	5 (16.7%)
Idiopathic thrombocytopenic purpura	2 (6.7%)
Scleroderma	1 (3.3%)
Rheumatoid arthritis	1 (3.3%)
Not identified	13 (43.3%)

Table 6 | Immunomodulation therapy for patients with type B insulin resistance syndrome

Immunomodulation therapy	No. patients
Steroid	12 (40.0%)
Helicobacter pylori eradication therapy	3 (10.0%)
Cyclosporine	2 (6.7%)
Azathioprine	1 (3.3%)
Human immunoglobulin	1 (3.3%)
None	16 (53.3%)

Table 7 | Physical findings for patients with insulin resistance syndromes

Physical findings	Type A	R-M/D	Type X	Type B
Characteristic facial appearance	4 (17%)	9 (90%)	5 (63%)	0 (0%)
Acanthosis nigricans	17 (74%)	7 (70%)	6 (75%)	5 (17%)
Hirsutism	9 (39%)	9 (90%)	5 (63%)	1 (3%)
Tooth hypoplasia	4 (17%)	4 (40%)	1 (13%)	0 (0%)
Scarce fat tissue	1 (4%)	8 (80%)	2 (25%)	0 (0%)
Fatty liver	0 (0%)	1 (10%)	3 (38%)	2 (7%)
Androgen excess	5 (22%)	5 (50%)	5 (63%)	0 (0%)

R–M/D, Rabson–Mendenhall/Donohue syndrome.

Table 8 | Triggers for diagnosis of insulin resistance syndromes

Trigger for diagnosis	Type A	R-M/D	Type X	Type B
Low birthweight	0 (0%)	5 (50%)	0 (0%)	0 (0%)
Physical findings	4 (17%)	2 (20%)	1 (13%)	1 (3%)[†]
Hyperglycemia	5 (22%)	3 (30%)	0 (0%)	20 (67%)
Hypoglycemia	0 (0%)	0 (0%)	0 (0%)	7 (23%)
Urinalysis at school	9 (39%)	0 (0%)	6 (75%)	0 (0%)
Diagnosis of relatives	3 (13%)	0 (0%)	1 (13%)	0 (0%)
Amenorrhea	1 (4%)	0 (0%)	0 (0%)	0 (0%)

R-M/D, Rabson–Mendenhall/Donohue syndrome. [†]One patient with mixed connective tissue disease was diagnosed on the basis of hand swelling.

Rabson–Mendenhall/Donohue syndrome and type B IRS showed the highest and second highest levels of hyperinsulinemia, respectively, and those in type A and type X IRS were similar. Fasting serum insulin levels for 26 of the 27 (96.3%) type A and type X IRS patients for whom such data were available were >30 μU/mL. By contrast, we measured the fasting insulin levels of 86 Japanese type 2 diabetes patients with a body mass index of <25 kg/m^2 and without insulin administration (age 61.3 ± 12.7 years, BMI 21.8 ± 3.1 kg/m^2), and found that they were all <30 μU/mL (1–26, 5.1 ± 4.0). A diagnosis of type A or type X IRS should thus be suspected in an individual with a fasting insulin level of >30 μU/mL and no other apparent cause of insulin resistance including obesity.

Type A IRS-like features in the absence of an *INSR* mutation are potentially attributable to defects in signaling downstream of the insulin receptor. Mutations in the gene for Akt2, a protein kinase that plays a key role in insulin action, and in the gene for TBC1D4, a substrate of Akt2 that contributes to the regulation of glucose transport, have been found to trigger the development of severe insulin resistance in humans[14,15]. PI 3-kinase mediates regulation of various actions of insulin[32].

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Mutations in *PIK3R1*, a gene that encodes a regulatory subunit of PI 3-kinase, were recently identified in individuals with SHORT syndrome[27]. Together with its characteristic body features, this syndrome is associated with the development of diabetes mellitus[33]. Furthermore, some individuals with *PIK3R1* mutations have been followed up as cases of insulin-resistant diabetes, not of SHORT syndrome[18], as were individuals with type X IRS in the present study. Given that five of the eight patients with type X IRS in our survey harbored *PIK3R1* mutations, *PIK3R1* is likely the most common responsible gene for severe insulin resistance triggered by a genetic defect in postreceptor insulin signaling. Four of the five patients with type X IRS with mutations in *PIK3R1* harbored the Arg649Trp mutation. Arg649 of the regulatory subunit of PI 3-kinase resides in a Scr-
homology-2 domain, a domain that is essential for the binding of the enzyme to insulin receptor substrates, and the Arg649Trp mutant protein inhibits the binding in a dominant negative manner[34]. Furthermore, forced expression of a dominant negative mutant of the regulatory subunit of PI 3-kinase has been shown to trigger glucose intolerance in mice[35].

We found that 60% of patients with type B IRS experienced hypoglycemia. Of note, the death of a patient with type B IRS from hypoglycemia has been reported[36–39]. The trigger for diagnosis of type B IRS was hypoglycemia in 23% of the present patients. Hypoglycemia is thus important both as a trigger of diagnosis and as a serious event that warrants careful attention in this syndrome. Although the precise mechanisms underlying occasional hypoglycemia remain unclear, one possible explanation is the presence of both inhibitory and stimulatory antibodies to the insulin receptor[8]. Autoantibodies associated with type B IRS are usually polyclonal[1,39], and such antibodies with different characteristics might exist simultaneously. Alternatively, dissociation of inhibitory antibodies from the insulin receptor by an unknown mechanism might result in a sudden burst of insulin signaling that gives rise to hypoglycemia.

In our survey, patients with type B IRS were defined as individuals who manifest hyperglycemia or hypoglycemia (or both) and possess autoantibodies to the insulin receptor. However, two such patients (patients 4 and 14) showed hypoglycemia without hyperinsulinemia. Given that such cases are not technically "insulin resistant," it might be inappropriate to classify them as type B IRS, with a new pathological categorization possibly being required. Regardless, healthcare providers should be aware that autoantibodies to the insulin receptor might induce hypoglycemia in the absence of insulin resistance or hyperinsulinemia.

The age at clinical diagnosis of type B IRS peaked in the 60s, and the male/female ratio was 19/11, suggesting that this syndrome occurs in mature individuals and that females are not at greater risk, in contrast to a previous study describing female predominance[13]. A total of 57% of patients were associated with concurrent autoimmune diseases, and 47% had been treated with immunomodulation therapy. Three patients with type B IRS had undergone eradication therapy for *H. pylori*, but only one of these patients, who also had ITP, responded to the treatment. Such therapy is thus unlikely to be effective for type B IRS patients in general. However, a patient with type B IRS and scleroderma was recently reported for whom *H. pylori* eradication eliminated the autoantibodies to the insulin receptor and markedly improved the effects of combined immune suppressants[40]. Given that ITP[41] and scleroderma[42] have been linked to *H. pylori* infection, type B IRS might be ameliorated by therapies effective for accompanying autoimmune diseases. Indeed, among the patients in our survey, the onset of type B IRS triggered the diagnosis of accompanying autoimmune diseases, and the treatment of these diseases also alleviated glycemic fluctuations. It seems reasonable to screen patients with type B IRS for other autoimmune diseases and to treat these accompanying disorders.

With regard to limitations, questionnaire-based surveys are associated with a certain level of inaccuracy in the collection of information. Of note, the effectiveness of therapies might not have been accurately estimated. In addition, we sequenced only the exons of *INSR* and *PIK3R1*, and therefore cannot exclude the possibility that some genetic abnormalities, including long deletions of the genes, were not identified. Finally, the cases of type A IRS and Rabson–Mendenhall/Donohue syndrome analyzed included suspected cases, given that genetic testing is not always carried out in the clinical setting.

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