



## Pedigree Investigation and Clinical Manifestation Analysis of Type A Insulin Resistance Syndrome: The Relationship between Insulin Level and Phenotype

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### Abstract

**Background:** Type A Insulin Resistance Syndrome (TAIRS) is a rare genetic disease, mainly caused by insulin receptor defects, characterized by a series of pathophysiological manifestations caused by severe insulin resistance. Unlike most people with insulin resistance, women with TAIRS are generally not overweight.

**Patient Description:** In this report, we describe a girl who presented with severe acanthosis nigricans, along with high levels of fasting insulin with normal plasma glucose, suggested severe insulin resistance. An INSR mutation (P1205L) was identified in the proband and her family. Although there are also heterozygous mutations in the INSR gene in the four members of the paternal lineage, the clinical manifestations are very heterogeneous.

**Conclusion:** The TAIRS family we reported had significant heterogeneity in genotype and clinical phenotype in the same genetic background and environment. We found that the clinical severity of family members was positively correlated with insulin levels. We believe that serum insulin levels may be able to assess the development of the disease.

### Introduction

Type A Insulin Resistance Syndrome (TAIRS) is a rare disorder characterized by severe insulin resistance, a condition in which the body's tissues and organs do not respond properly to the hormone insulin. TAIRS is often caused by mutations in the *INSR* gene, which leads to insulin receptor dysfunction [1]. The condition usually presents at post puberty and is characterized by insulin resistance, acanthosis nigricans and hyperandrogenism, but without obesity or lipodystrophy [1,2]. A number of different mutations in the insulin receptor gene have been reported in patients with TAIRS. Although this syndrome is inherited as autosomal recessive traits, a clear correlation between genotype and phenotype has not yet been established.

In this report, we describe a girl who presented with severe acanthosis nigricans, along with high levels of fasting insulin with normal plasma glucose, suggested severe insulin resistance. An *INSR* mutation (P1205L) was identified in the proband and his father, grandfather and little aunt. Interestingly, her family members shared the same mutation but showed different clinical course.

### Case Presentation

The proband, a girl of 12 years old, was referred to our hospital because of acanthosis nigricans and hirsutism more than 11 years and change voice for 4 months. She was born with birth weight of 2,650 g (-1.65 SDS), without significant past medical or developmental concerns. The parents are Chinese and nonconsanguineous. With age, hirsutism and acanthosis nigricans were more pronounced. Her pubic hair appeared and increased rapidly eight months ago and began to change voice 4 months ago. No symptoms of polydipsia and polyuria. At presentation, she was not obese, but showed severe skin pigmentation and hirsutism. She also existed acanthosis nigricans at the neck and axilla. Pigmented spots were seen on the lateral side of the left thigh and the right lower abdomen. Body Mass Index (BMI) was 16.21 kg/m<sup>2</sup> (height 149 cm and weight 36 kg), Blood Pressure was 119/78 mmHg. Her breasts were Tanner 4 and pubic hair was Tanner 4. Laboratory tests revealed the following; Hemoglobin A1C (HbA1C), 6.9% (normal: <6.3%); Fasting Plasma Glucose (FPG) 4.3 mmol/L; serum insulin 258.9 mIU/L; C-peptide 3.47 ng/mL; Oral Glucose Tolerance Test (OGTT) and insulin, c peptide release test suggested that children with diabetes and severe hyperinsulinemia

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**Table 1:** OGTT, insulin and C peptide releasing test of proband.

	0 min	30 min	60 min	90 min	120 min
Blood glucose (mmol/L)	4.3	9.3	11.7	12.9	13
Insulin (mIU/L)	259	874.5	1219	>1500	>1500
C peptide (ng/mL)	3.47	9.42	13.33	18.05	18.77

(insulin resistance) (Table 1). Islet associated autoantibodies were absent. Urine testing showed no ketonuria, proteinuria or glucosuria. Blood routine, blood gas analysis, thyroid function, liver function, Human Chorionic Gonadotropin (HCG) were normal. Her serum levels of cortisol, adrenocorticotropic hormone, growth hormone and prolactin were normal. Gonadotropin baseline values, including Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), and Estradiol (E2) are normal levels. Testosterone (T), 128.7 ng/dl; Dehydroepiandrosterone Sulfate (DHEAS), 76.45 µg/ml; Androstenedione, 5.03 ng/ml were significantly higher than girls of the same age. Bone age is about 13 years old. Pelvic ultrasound showed the size of uterus is about 3.3 cm<sup>3</sup> × 2.1 cm<sup>3</sup> × 3.0 cm<sup>3</sup>, and the thickness of endometrium is about 0.5 cm; the left ovary is 3.8 cm<sup>3</sup> × 2.0 cm<sup>3</sup> × 2.8 cm<sup>3</sup>, the right ovary is 4.2 cm<sup>3</sup> × 3.1 cm<sup>3</sup> × 2.2 cm<sup>3</sup>. Ultrasound scan revealed findings of polycystic ovary syndrome (PCOS) with bulky ovaries and small peripheral follicles.

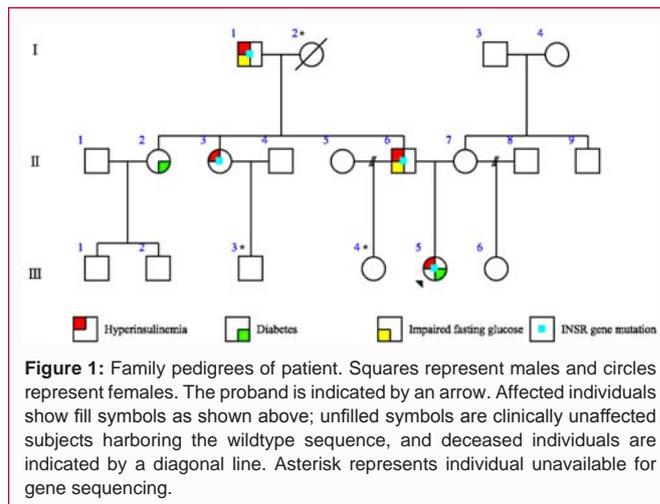
Based on the clinical manifestations and laboratory findings of hirsutism, acanthosis, severe insulin resistance, hyperglycemia, hyperandrogenism, we clinically diagnosed TAIRS. We first gave metformin hypoglycemic therapy. As a result of drug-induced diarrhea in patient, we changed to pioglitazone treatment. To control hyperandrogenism, we administered flutamide tablets. Because of concerns about drug side effects, flutamide was changed to spironolactone. After 6 months of treatment, the patient's neck acanthosis nigricans and lower voice were better than before. Review fasting blood glucose fluctuation in 3.8 mmol/l ~ 4.0 mmol/l, fasting insulin reduced to 79.5 mIU/L, HbA1c 6.5%. After 9 months of treatment, the child menstruation menarche, but rare and irregular. Review LH 4.77 mIU/ml, FSH 4.0 mIU/ml, T 107.5 ng/dl, E2 51.5 pg/ml, DHEAS 147.6 µg/ml, Androstenedione 6.4 ng/ml, HbA1c 5.7%, fasting insulin 85.0 mIU/. At present, the control of blood glucose is stable, but the control of hyperandrogenism is poor.

Consent for genetic investigation was obtained and results confirmed heterozygous c.3614C>T/p.P1205L mutation in *INSR* gene mutation. The family map shown in Figure 1. The proband's mother (II-7), maternal grandfather (I-3), grandmother (I-4), uncle (II-9) and half-sisters (III-4, III-6) have no history of diabetes (Figure 1). Her father (II-6) and grandfather (I-1), with the P1205L mutation, had impaired fasting blood glucose for 4 and 3 years respectively. Older aunt (II-2) has a 10-year history of DM and is currently treated with Metformin and Acarbose. The proband's little aunt (II-3), a lean

**Table 2:** Basic clinical information in family members.

	Age	FG (mmol/L)	2h PG (mmol/L)	HbA1C (%)	FINS (mIU/L)	CP (ng/ml)	<i>INSR</i> gene mutation	Phenotype
Grandfather	77	6.4	7	6.2	46.5	ND	+	IFG
Father	49	6.1	6.5	6.1	48	1.4	+	IFG
Proband	12	4.3	13	6.9	258.9	3.5	+	DM
Mother	50	5.17	ND	6.1	8	0.9	-	-
Elder aunt	51	11.5	ND	8.5	7.5	ND	-	DM
Little aunt	46	4.6	5.4	5.5	32.3	1.1	+	-

FG: Fasting plasma glucose; 2hPG: 2 hours after OGTT; HbA1C: Glycosylated hemoglobin; FINS: Fasting insulin; IFG: Impaired fasting glucose; CP: C peptide; DM: Diabetes mellitus; ND: Not done.



46-year-old woman, also carries the P1205L mutation. Whereas she exhibited an exaggerated increase in serum insulin levels during the OGTT, she manifested neither common clinical features of type A insulin resistance, including dermatologic or gynecologic disorders, nor glucose intolerance (Table 2). The basic clinical information and blood glucose and insulin values of 6 core family members are shown in Table 2. Father family of three generations all live in Zhejiang Shengzhou rural areas, similar living environment, eating habits and the same way, birth weight in the normal range, with no special hobby.

### Discussion

The child is adolescent girl with typical clinical manifestations of TAIRS, namely, severe insulin resistance, acanthosis, hairy, polycystic ovary, hyperandrogenism. The detection of *INSR* gene revealed a heterozygous mutation of c.3614C>T/p.P1205L, and the diagnosis of TAIRS was clear. The Insulin Receptor (IR) is a transmembrane receptor that is activated by insulin, IGF-I, IGF-II and belongs to the large class of tyrosine kinase receptors [3]. Metabolically, Binding of insulin or other ligands to this receptor activates the insulin signaling pathway, which regulates glucose uptake and release, as well as the synthesis and storage of carbohydrates, lipids and protein. The insulin receptor is encoded by a single gene *INSR*, from which alternate splicing during transcription results in either IR-A or IR-B isoforms [4]. Downstream post-translational events of either isoform result in the formation of a proteolytically cleaved α and β subunit, which upon combination are ultimately capable of homo or hetero-dimerisation to produce the ≈320 kDa disulfide-linked transmembrane insulin receptor [4]. The binding of ligand to the α-chains of the IR ectodomain induces structural changes within the receptor leading to autophosphorylation of

various tyrosine residues within the intracellular TK domain of the  $\beta$ -chain, eventually promoting downstream processes involving blood glucose homeostasis [5]. The Insulin Receptor is a type of tyrosine kinase receptor, in which the binding of an agonistic ligand triggers autophosphorylation of the tyrosine residues. The addition of the phosphate groups generates a binding site for the insulin receptor substrate (IRS-1), which is subsequently activated *via* phosphorylation. The activated IRS-1 initiates the signal transduction pathway and binds to phosphoinositide 3-kinase (PI3K), in turn causing its activation.

TAIRS can be expressed as autosomal recessive inheritance or autosomal dominant inheritance [6-8]. The *INSR* gene c.3614 C>T/p.1205L heterozygous mutation was found in 4 individuals in this family, which was autosomal dominant. The phenotype of heterozygous P1205L differed substantially among the current family members. Although the proband showed hirsutism, acanthosis, severe insulin resistance, and newly discovered diabetes. Her father and grandfather only presented impaired fasting glucose and relatively mild hyperinsulinemia. In addition, her little aunt did not show insulin resistance after fasting. Takahashi I et al. [9] consider this difference may be conditioned by heredity and environment. The lifestyle for children has changed over the last few decades in Japan [9]. However, we report that the three generations of the family are living in the rural areas of Zhejiang. Living environment, eating habits and manners are similar. The birth weights were all within the normal range, and no special habits were found. Therefore, it has not been found that living environment and dietary changes are closely related to the differences in clinical phenotypes; this view is not supported.

In this study, we found that the fasting insulin levels of 4 individuals with *INSR* gene c.3614 C>T/p.1205L heterozygous mutation increased, especially in probands. The proband insulin levels (OGTT 0 min, 90 min, and 120 min) were 258.9 mIU/L, >1500 mIU/L, and >1500 mIU/L, respectively. Testosterone from the ovaries and body tissues, as well as androgen (DHEAS and androstenedione) from the adrenal reticularis are significantly elevated. She showed severe hairy and black echinoderms. Grandpa and his father's fasting insulin were 46.5 mIU/L and 48.0 mIU/L, and had 3 and 4 years of impaired fasting glucose, respectively. Fasting insulin in little aunt was 32.3 mIU/L and the age was relatively small. All patients with insulin resistance syndrome have hyperinsulinemia [10-12]. We found that the degree of insulin resistance is closely related to the heterogeneity of the clinical phenotype of the *INSR* gene mutation. Under the same genetic background and environment, the higher the serum insulin level, the more serious the clinical performance.

Mutations in the insulin receptor gene lead to insulin and its receptor binding disorders, the target organ response to insulin decreased, causing feedback hyperinsulinemia. High insulin levels in turn reduce the synthesis of sex hormone-binding globulin in the liver, and at the same time stimulate the synthesis of androgen in ovarian follicle endometrial cells, adrenal glands, and peripheral tissues, resulting in hyperandrogenism. The higher the serum androgen level, the more severe the insulin resistance and metabolic abnormalities [13,14]. The finding that DHT exposure to cultured islets up-regulates *Ins1* and *Ins2* mRNA suggests insulin is a physiological target for DHT and that androgens can directly regulate the transcription of insulin [15]. Therefore, insulin resistance and hyperandrogenism promote each other in the development of disease in TAIRS. Hyperinsulin promotes the synthesis of androgen and metabolic

disorders, and high androgen can also promote insulin secretion and increase insulin resistance and metabolic abnormalities, causing a vicious circle. Based on the above view, we treated rosiglitazone, an insulin sensitizer. After treatment, our patient, the level of insulin was significantly decreased, blood glucose was stable, but the level of androgen was not significantly reduced, which was consistent with many other reports [16]. This suggests that the TAIRS induced by the *INSR* gene mutation may be different from the polycystic ovary syndrome in the metabolic pathways between the insulin resistance and hyperandrogenemia, even if the patients have PCOS.

Management of patients with severe IR should aim to prevent long-term complications from diabetes and reduce the effects of hyperandrogenism [2]. Wei [17] considered that beta-cell function ultimately deteriorates and patients are at risk of long-term complications of diabetes, although the timeframe is unclear. After treatment, our patient, the level of insulin was significantly decreased, blood glucose was stable, but the level of androgen was not significantly reduced, which is consistent with Wei report [17]. Although many reports suggest that TAIRS can present in early adolescence and is more frequently diagnosed in young adult women with features of hyperandrogenism [1,2]. However, our patients developed clinical manifestations of insulin resistance and hyperandrogenism (pigmentation and hirsutism) in early childhood, which is aggravated during adolescence. Impaired glucose tolerance or diabetes is often asymptomatic and only recognized through subsequent biochemical screening. The presence of severe hyperandrogenism in the non-obese patient should alert pediatricians to consider severe IR as a possible diagnosis. Management of patients with severe IR should aim to prevent long-term complications from diabetes and reduce the effects of hyperandrogenism [2]. In addition, maintenance of healthy weight and BMI play a significant role in glucose homeostasis [17].

## Conclusion

We report a family of TAIRS for the heterozygous mutation in the *INSR* gene. Although there are also heterozygous mutations in the *INSR* gene in the four members of the paternal lineage, the clinical manifestations are very heterogeneous. Phenotypic heterogeneity correlates with insulin levels. The treatment of hyperandrogenism in children with TAIRS is still difficult. Further study of the pathogenesis and metabolic pathways of TAIRS may lead to a new therapeutic target of hyperandrogenism.

## Competing Interest

The authors declare that there is no conflict of interest relevant to this manuscript.

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