ACCSCIENCE PUBLISHING

Gene & Protein in Disease

CASE REPORT

A novel presentation of a His1157Arg *INSR* mutation in male half-siblings with type A insulin resistance: A case report

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Abstract

Type A insulin resistance, a rare disorder resulting from mutations in the *INSR* gene, exhibits a wide range of clinical presentations. We report two male half-siblings with a His1157Arg missense mutation in exon 19 of the *INSR* gene. Patient 1 presented with hyperglycemia and features resembling type 1 diabetes, without acanthosis nigricans. In contrast, patient 2 exhibited characteristics typically seen in children diagnosed with type 2 diabetes, including obesity and acanthosis. Genetic testing confirmed the shared pathogenic mutation. Their divergent phenotypes underscore the heterogeneity of type A insulin resistance and highlight the critical role of genetic testing in atypical diabetes cases. Targeted therapy with metformin, glucagon-like peptide-1 receptor agonists, and sodium-glucose co-transporter 2 inhibitors improved glycemic control in both patients.

Keywords: Insulin resistance; Insulin receptor; *INSR*; Atypical diabetes; Type A insulin resistance

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1. Introduction

Type A insulin resistance is a rare condition caused by mutations in the *INSR* gene, which encodes the insulin receptor protein.[1] The insulin receptor consists of α and β subunits that play a crucial role in insulin signalling.[1] Mutations in the tyrosine kinase domains of the β subunit, encoded by exons 12–22 of the *INSR* gene, impair receptor function, leading to hyperinsulinemia and hyperglycemia.[1-3] This report presents two male half-siblings with a His1157Arg missense mutation in exon 19, a dominant-negative mutation associated with reduced tyrosine kinase activity. Their divergent clinical presentations highlight the heterogeneity of type A insulin resistance and underscore the importance of genetic testing in atypical diabetes cases.

2. Case presentation

2.1. Patient 1

A 14-year-old male presented with polyuria, polydipsia, and hyperglycemia (glycated hemoglobin [HbA1c] 8.8%) without ketoacidosis. He had a BMI around the 50th percentile and no reported weight loss. Initially diagnosed with type 1 diabetes, he was started

on insulin therapy. Despite initial glycemic improvement (HbA1c 7.2%), his insulin requirements escalated to 2–2.5 units/kg/day, and glycemic control deteriorated (HbA1c >10%). Metformin was added, resulting in modest glycemic improvement (HbA1c 7–9%).

At age 19, after being lost to follow-up and self-discontinuing insulin and metformin, he presented with hyperglycemia (HbA1c 10.9%), an elevated insulin level (92.2 μIU/mL), and negative pancreatic autoantibodies. A monogenic diabetes panel, excluding *INSR*, was negative. Subsequent targeted testing revealed a pathogenic His1157Arg mutation in the *INSR* gene. Insulin was discontinued, and metformin monotherapy improved his HbA1c to 7.2%. The addition of a sodium-glucose co-transporter 2 (SGLT-2) inhibitor and pioglitazone further enhanced glucose control.

2.2. Patient 2

A 9-year-old male presented with obesity, hyperglycemia (HbA1c 9.1%), and severe acanthosis nigricans. With a sedentary lifestyle and suboptimal diet, he was diagnosed with type 2 diabetes and treated with metformin, dietary changes, and lifestyle modifications. BMI improved to the 85th percentile over several years of treatment, acanthosis resolved, and HbA1c decreased to 5.2%, though it subsequently rose to 7.3%. Family history revealed that patient 2 and patient 1 shared the same mother, and sequencing of the *INSR* gene confirmed that patient 2 carried the same His1157Arg mutation. Metformin was continued, and glucagon-like peptide-1 (GLP-1) receptor agonist and SGLT-2 inhibitor were added, reducing HbA1c to 5.1%.

3. Discussion

The *INSR* gene, located on chromosome 19, encodes the insulin receptor, a tyrosine kinase receptor on cell membranes. In normal insulin signaling, insulin binds to the receptor, activating intrinsic tyrosine kinase activity, which causes phosphorylation of insulin receptor substrates (IRS). This triggers downstream pathways resulting in glucose uptake, glycogen synthesis, and cell growth. Mutations in the kinase domain prevent IRS phosphorylation and disrupt downstream signaling. Mutations in the tyrosine kinase domains of the β subunit (exons 12–22) impair insulin signaling, causing a spectrum of insulin resistance syndromes, ranging from mild (type A insulin resistance) to more severe forms (Rabson–Mendenhall syndrome and Donahue syndrome).[1,3]

Type A insulin resistance typically presents in childhood or early adulthood with hyperglycemia, elevated serum insulin, and acanthosis nigricans. Acanthosis nigricans results from insulin cross-stimulation of the insulin-like growth factor receptor in the skin, leading to keratinocyte and dermal fibroblast proliferation, which causes thickening and hyperpigmentation. The His1157Arg mutation in exon 19 of *INSR* is a dominant-negative mutation that reduces tyrosine kinase activity in the insulin receptor.[2,4] disrupting downstream insulin signaling. This mutation has previously been identified only in females.[4,5] Patient 1 presented atypically, without acanthosis nigricans and with a normal BMI, resembling type 1 diabetes. In contrast, patient 2 exhibited classical features of type A insulin resistance with obesity and acanthosis, though he was initially diagnosed with type 2 diabetes. These divergent presentations highlight the heterogeneity of the condition, even among half-siblings, and the potential for misdiagnosis as type 1 or type 2 diabetes. Table 1 compares the clinical and laboratory characteristics of the two cases.

Differing environmental or genetic influences (in this case, being raised separately with different fathers) may contribute to the divergent presentations, although heterogenous symptomatology has previously been reported in individuals with identical *INSR* mutations.[6,7] Genetic testing was instrumental in confirming the diagnosis and enabling targeted treatment to improve glycemic control. This case also emphasizes the need to consider monogenic diabetes in lean patients who require high insulin doses or in siblings of individuals with confirmed *INSR* mutations. We suspect that many patients with monogenic forms of diabetes remain undiagnosed or misdiagnosed as having either type 1 or type 2 diabetes. Early identification of *INSR* mutations allows for more appropriate therapies, such as metformin, GLP-1 receptor agonists, and SGLT-2 inhibitors to improve glycemic control and reduce insulin resistance.[8-10] Nishikage *et al*. have also proposed a method to distinguish hyperglycemia due to *INSR* mutations from type 2 diabetes.[11]

Table 1. Comparison of clinical and laboratory features in cases of type A insulin resistance

Feature	Patient 1	Patient 2
Acanthosis nigricans	–	+
Obesity	–	+
Age at presentation (years)	14	9
HbA1c at presentation (%)	8.8	9.1
Serum insulin (non-fasting)	92.2 mIU/mL[a]	478 mIU/mL[b]

Notes: [a]Measured after being lost to follow-up and discontinuing exogenous insulin; [b]Measured at initial presentation.
Abbreviation: HbA1c: Glycated hemoglobin.

4. Conclusion

Identification of an *INSR* mutation in two male half-siblings provided clarity and supported effective treatment. This case underscores the importance of considering monogenic causes of diabetes in patients with atypical presentations and emphasizes the utility of genetic testing in informing personalized therapeutic strategies and guiding family screening.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Investigation: Evan Los
Writing–original draft: All authors
Writing–review & editing: All authors

Ethics approval and consent to participate

The East Tennessee State University Institutional Review Board and the Ballad Health Institutional Review Board determined that this case report does not constitute "Human Subjects Research." The patients and guardians provided verbal consent to participate in the study.

Consent for publication

Verbal informed consent was obtained from the patients and their legal guardians for the publication of this report.

Availability of data

Not applicable.

Further disclosure

This case was originally presented in oral form (Type A insulin resistance can be misdiagnosed as type 1 or type 2 diabetes - A cautionary tale) by Kaci Wirthwein at the American Diabetes Association 84th Scientific Sessions (Orlando, Florida) on [June 21, 2024].

References

1. Ogawa W, Araki E, Ishigaki Y, *et al*. New classification and diagnostic criteria for insulin resistance syndrome. *Diabetol Int*. 2022;13(2):337-343.
doi: 10.1007/s13340-022-00570-5

2. Angelidi AM, Filippaios A, Mantzoros CS. Severe insulin resistance syndromes. *J Clin Invest*. 2021;131(4):e142245.
doi: 10.1172/JCI142245

3. Ardon O, Procter M, Tvrdik T, Longo N, Mao R. Sequencing analysis of insulin receptor defects and detection of two novel mutations in INSR gene. *Mol Genet Metab Rep.* 2014;1:71-84.
doi: 10.1016/j.ymgmr.2013.12.006

4. Vambergue A, Lautier C, Valat AS, Cortet-Rudelli C, Grigorescu F, Dewailly D. Follow-up study of two sisters with type A syndrome of severe insulin resistance gives a new insight into PCOS pathogenesis in relation to puberty and pregnancy outcome: A case report. *Hum Reprod*. 2006;21(5):1274-1278.
doi: 10.1093/humrep/dei455

5. Sanderson EE, Shah M, Hooper AJ, Bell DA, Choong CS. Monogenic diabetes due to an INSR mutation in a child with severe insulin resistance. *Endocrinol Diabetes Metab Case Rep.* 2022;2022(1):1-5.
doi: 10.1530/EDM-21-0114

6. Takahashi I, Yamada Y, Kadowaki H, *et al*. Phenotypical variety of insulin resistance in a family with a novel mutation of the insulin receptor gene. *Endocr J*. 2010;57(6):509-516.
doi: 10.1507/endocrj.k09e-339

7. Collin-Chavagnac D, Saint-Martin C, Bedidi L, *et al*. Insulin receptor variants: Extending the traditional Mendelian spectrum. *Genet Med*. 2025;27(6):101404.
doi: 10.1016/j.gim.2025.101404

8. Hirota Y, Kakei Y, Imai J, *et al*. A multicenter, open-label, single-arm trial of the efficacy and safety of empagliflozin treatment for refractory diabetes mellitus with insulin resistance (EMPIRE-01). *Diabetes Ther*. 2024;15(2):533-545.
doi: 10.1007/s13300-023-01526-x

9. Martínez-Montoro JI, Pinzón-Martín JL, Damas-Fuentes M, Feràndez-Valero A, Tinahones FJ. Combination therapy with semaglutide and dapagliflozin as an effective approach for the management of type A insulin resistance syndrome: A case report. *Front Endocrinol (Lausanne)*. 2022;13:838887.
doi: 10.3389/fendo.2022.838887

10. Nagashima S, Wakabayashi T, Saito N, *et al*. 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(5):1363-1365.
doi: 10.1111/jdi.13241

11. Nishikage S, Hirota Y, Takayoshi T, *et al*. Utility of the C-peptide/insulin molar ratio for distinguishing type A insulin resistance syndrome from type 2 diabetes. *J Clin Endocrinol Metab*. 2025;110(10):e3383-e3390.
doi: 10.1210/clinem/dgaf043