

Case report

## Homozygous mutation in the insulin receptor gene and mild form of insulin resistance syndrome; a case report

**Running title:** Homozygous mutation and mild form of insulin resistance

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### What is already known on this topic?

Insulin receptor mutations lead to heterogeneous disorders; as severe as Donohue syndrome or as mild as “type A insulin resistance syndrome”. Patients with severe disorders are homozygous or compound heterozygous mutations. Generally patients with type A insulin resistance syndrome have been found to be heterozygous mutations. Homozygous insulin receptor gene mutations may rarely be responsible for mild type insulin resistance syndrome.

### What this study adds?

We emphasized that homozygous insulin receptor mutations may also cause mild clinical forms and we reported a novel homozygous mutation p.Leu260Arg on exon 3 on *INSR* gene in a patient with type A insulin resistance syndrome.

### Abstract

Insulin receptor mutations lead to heterogeneous disorders; as severe as Donohue syndrome or as mild as “type A insulin resistance syndrome”. Patients with severe disorders are homozygous or compound heterozygous mutations. Generally patients with type A insulin resistance syndrome have been found to be heterozygous mutations, homozygous type mutations may rarely be responsible for this disease. We reported a novel homozygous mutation p.Leu260Arg on exon 3 on *INSR* gene in a patient with type A insulin resistance syndrome. In this article, we report an adolescent with type A insulin resistance syndrome due to a novel homozygous mutation on the *INSR* gene and detailed her medical follow-up. Different mutations in the *INSR* gene causes different phenotype and different inheritance pattern also, our report is important to making disease mechanism understand and also helping genetic counseling process.

**Keywords:** Hirsutism, Insulin resistance, Insulin receptor gene,

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### Introduction

Functional insulin receptor (*INSR*) is crucial for intracellular effects of insulin and its mutations lead to genetic severe insulin resistance. It is a transmembrane protein and which is a member of the receptor tyrosine kinase family. This receptor is a heterotetramer and consisting of two  $\alpha$  and  $\beta$  subunits.  $\alpha$  subunits are extracellular, whereas the  $\beta$  subunits begin on the extracellular side of the membrane and then traverse the membrane into the cytoplasmic region that contains the tyrosine kinase activity. Activation of the *INSR* requires transautophosphorylation of one  $\beta$  subunit by the other  $\beta$  subunit. A single gene *INSR* encodes for both subunits, which is located on chromosome 19. Each allele of this gene encodes one  $\alpha\beta$  half-receptor and two of them form  $\alpha\beta\beta\alpha$  heterotetrameric insulin receptor. This phenomenon explains how heterozygous mutations resulting in impaired  $\beta$  subunit tyrosine kinase activity (1-2).

Insulin receptor mutations lead to heterogeneous disorders; as severe as Donohue syndrome (leprechaunism) and Rabson-Mendenhall syndrome and as mild as “type A insulin resistance syndrome”. Patients with severe disorders are homozygous or compound heterozygous for these mutations (3,4). Generally patients with type A insulin resistance syndrome have been found to have heterozygous mutations however, homozygous type mutations may rarely be responsible for this disease (5-7). Type A insulin resistance syndrome manifests itself in peripubertal period, as oligomenorrhea and hyperandrogenism with acanthosis nigricans. In this article, we report an adolescent with type A insulin resistance syndrome due to a novel homozygous mutation on the *INSR* gene and detailed her 3 years medical follow-up.

### Case Report

A 12-year-old girl was admitted to the pediatric endocrinology department for excess hair growing on her body. This complaint has been emerged over the last year. In the family history of the patient, her parents had no consanguinity and both parents were healthy. Her birth weight was normal and her past medical history was uneventful. She had a severe hirsutism (Modified Ferriman-Gallwey Score was 30), acneiform rash on her face and severe acanthosis nigricans was observed in the axilla, neck and antecubital area (Figure 1A-1B). Her blood pressure was 110/70 mmHg. Her height was 156.5 cm (70th percentile), weight was 68.4 kg (99th percentile), and body mass index was 27.9 kg/m<sup>2</sup> (98th percentile) at the admission. Her pubertal development were Tanner stage IV and her bone age was 13.5 years old. There was no history of spontaneous menarche. Laboratory examinations revealed that elevated fasting insulin level with normal fasting glucose.

Glycohemoglobin level and oral glucose tolerance test results showed that she was in prediabetic state with marked hyperinsulinemia. Despite the severe hyperinsulinemia she had normal triglyceride, high-density lipoprotein (HDL) cholesterol and sex hormone binding globulin (SHBG) level and there was not hepatosteatosis on ultrasonographic evaluation. Her gonadotropin levels revealed that luteinizing hormone (LH) dominance with increased testosterone level. There was a polycystic ovary appearance on ultrasonographic evaluation. Her laboratory examinations results are detailed in table 1. Through the findings of clinical and laboratory examination type A insulin resistance syndrome was considered and INSR mutation analyses were planned. DNA Sanger Sequence analyses of the INSR all coding exons showed that a novel homozygous mutation NM\_000208.4 c.779 T>G (p.Leu260Arg) in exon 3 (Figure 2). Genetic analysis of the parents demonstrated both were carrier of the same mutation. There were no clinical or biochemical hyperandrogenism and disorder of glucose metabolism on her mother, but her father was not detailed due to extenuating circumstances.

In her treatment first we started metformin (we increased the dose gradually at 2 gram/day) with life style modification. She could not do life style modification continuously during whole therapy process. After 1 year this therapy, we added oral contraceptive (OCP) (2 mg cyproterone acetate plus 35 microgram ethinyl estradiol) treatment because increasing hirsutism. We aimed with this treatment procedure to suppress ovarian hyperandrogenism and to be benefited the anti-androgenic potential of cyproterone acetate. One year after treatment her hirsutism score markedly decreased (Figure 1C). Menarche occurred after this treatment.

During her clinical follow-up we added basal-bolus insulin regimen in her therapy because of marked hyperglycemia especially postprandial period and high glycohemoglobin level (8.6%). HbA1c value decreased to 7% with 6 months basal-bolus insulin treatment. During the follow-up, we discontinued bolus insulin and continued only with basal insulin and metformin. The mean HbA1c was 7.4% at one-year follow-up. Parents of the patients provided informed consent.

**Ethical approval:** The conducted research is not related to either human or animals use.

### Discussion

In adolescent period a patient with hyperandrogenism and severe insulin resistance whose findings could not be explained by other reasons such as obesity, should remind genetic insulin resistance syndromes to the clinicians. *INSR* gene mutations should be kept in mind in patients with severe insulin resistance but without metabolic dyslipidemia, low SHBG level and hepatosteatosis. There were many clues in clinical and laboratory features of our patient about the *INRS* mutation. Metabolic dyslipidemia (hypertriglyceridemia and low HDL-cholesterol levels) and steatohepatitis are closely associated with prevalent forms of insulin resistance (8). Key factor in the development of metabolic dyslipidemia and hepatic steatosis is postreceptor hepatic insulin resistance. Reduced liver fat synthesis plays a key role in the protection from dyslipidemia observed in patients with insulin receptoropathy (9). Eventually absence of metabolic dyslipidemia and fatty liver in a patient with severe insulin resistance like our patients is suggestive of a primary insulin receptor mutation.

There are no obvious genotype-phenotype correlations for *INSR* mutations, It has been suggested that the homozygous mutations of the  $\alpha$ -subunit cause more severe clinical features, whereas heterozygous  $\beta$ -subunit mutations lead to milder forms (1,3). However, this is not the case in many patients. Many type A insulin resistance patients with  $\alpha$ -subunit mutations has been reported like our patients (5-7).

Generally patients with type A insulin resistance syndrome have been found to be heterozygous mutations however, homozygous type mutations may rarely be responsible for this disease. Nakashima N. et al. previously described a Japanese patient diagnosed as type A resistant insulin resistance syndrome with homozygous mutation (7). Later same mutation was detected in a patient from Morocco. Homozygous mutation was reported in 3 of 8 type A resistance syndrome patients in another series. Interestingly all Type A insulin resistance syndrome patients have  $\alpha$  subunit mutations whose have homozygous mutation (6). We detected a novel homozygous mutation on exon 3 (p.Leu260Arg). Mutation that leucine instead of proline on the same codon was reported previously in a family. Homozygous form of this mutation (p.Leu260Pro) has been associated with leprechaunism (10). It was concluded that mutation is in this region which functionally links the insulin binding site on the  $\alpha$ -subunit with the tyrosine kinase domain on the  $\beta$  subunit (10). It was observed that heterozygous form of p.Leu260Pro mutation is associated with normal phenotype with mild insulin resistance (1). Also it was reported that different missense mutations in the same codon can cause different phenotypes.

Currently available therapies of genetic insulin resistance syndromes are nonspecific. Dietary changes and exercise in addition to drug therapy (metformin with or without insulin) have been mainstay to reduce the insulin resistance (8). Commonly, patient with mild *INSR* defects present peripubertally as oligomenorrhea and hyperandrogenism with acanthosis nigricans and sometimes misdiagnosed as polycystic ovary syndrome (11). At presentation, diabetic hyperglycemia has often yet to develop as our patient (8). Hirsutism treatment is difficult in these cases, but we have received good response to cyproterone acetate treatment (11).

We reported a novel homozygous mutation p.Leu260Arg on exon 3 on *INSR* gene in a patient with type A insulin resistance syndrome. However, the mutation that makes the patient interesting is that it is homozygous. Because of different mutations in the *INSR* gene causes different phenotype and different inheritance pattern also, our report is important to making disease mechanism understand and also helping genetic counseling process. In conclusion, homozygous insulin receptor mutations rarely, as in our patient, might be associated with type A insulin resistance.

### Ethics

**Informed Consent:** Informed consent was obtained from the patient and mother

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: Bülent Hacıhamdioğlu, Kenan Delil Data Collection and Processing: Bülent Hacıhamdioğlu, Kenan Delil, Elif Gülşah Baş, Analysis and Interpretations: Bülent Hacıhamdioğlu, Kenan Delil, Elif Gülşah Baş, Literature Search: Bülent Hacıhamdioğlu, Kenan Delil, Elif Gülşah Baş.

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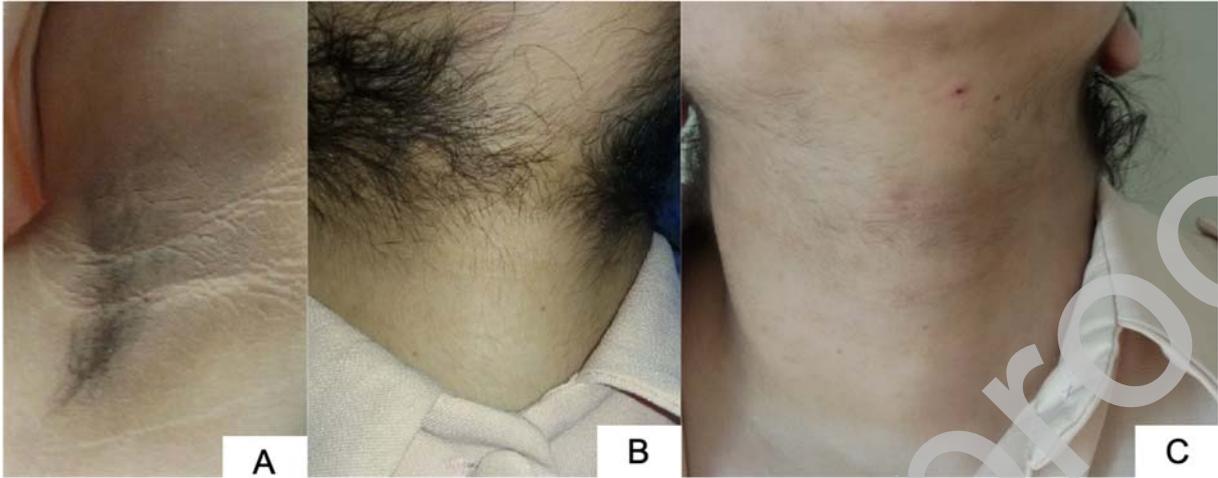
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**Table 1.** Laboratory data of a patient

<b>Parameter</b>	<b>Result (Normal)</b>
Glucose	74 mg/dl
Insulin	217 mIU/ml (N<20)
Glycohemoglobin	%5.74
OGTT 120 minute glucose	162 mg/dl
OGTT 120 minute insülin	893.5 mIU/ml
Triglyceride	59 mg/dl
High-Density Lipoprotein-cholesterol	71 mg/dl
Total-cholesterol	144 mg/dl
ALT/AST	15/15 IU/l
FSH	6.5 mIU/ml
LH	14.4 mIU/ml
Total testosterone	190 ng/dl (N<55)
DHEA-SO4	104 mcg/dl (N<350)
SHBG	92.07 nmol/l (N: 17-155)

\*OGTT; oral glucose tolerance test, ALT; alanine aminotransferase, AST; aspartate aminotransferase, FSH; follicle-stimulating hormone, LH; luteinizing hormone, DHEA-SO4; dehydroepiandrosterone sulphate, Sex hormone binding globuline (SHBG)

**Figure 1.** Clinical features of patient. A. severe acanthosis nigricans. B. Hirsutism before and treatment and C. after treatment



**Figure 2.** DNA Sequencing Chromatogram of the patient. Arrow showed homozygous *NM\_000208.4 c.779 T>G* (*p.Leu260Arg*) mutation in the exon 3 of *INSR* Gene

