Novel Insights from Clinical Practice

HORMONE RESEARCH IN PÆDIATRICS

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An Insulin-Like Growth Factor-I Receptor Defect Associated with Short Stature and Impaired Carbohydrate Homeostasis in an Italian Pedigree

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Established Facts

- Different mutations in the insulin-like growth factor-I (IGF-I) receptor *(IGF1R)* gene have been associated with impaired prenatal and postnatal growth.
- The IGF-I/IGF1R system is implicated in the regulation of glucose metabolism by modulating insulin sensitivity and insulin secretion.

Novel Insights

- This study reports a novel mutation in the *IGF1R* gene in four family members associated with a variable degree of prenatal and postnatal growth impairment.
- We also observed an association between the IGF1R defect and alterations in carbohydrate metabolism, characterized by a variable phenotype ranging from normal glucose tolerance in the presence of insulin resistance to impaired glucose tolerance and fasting hyperglycemia in association with both insulin resistance and disturbed β-cell function.

Key Words

Insulin-like growth factor-I receptor · Glucose metabolism · Insulin sensitivity · Insulin secretion · Short stature · Small for gestational age

Abstract

Background: Mutations in the insulin-like growth factor-I (IGF-I) receptor (IGF1R) have been associated with prenatal and postnatal growth retardation. However, little is known about potential effects of mutations in the IGF1R on carbohydrate homeostasis. ***Methods:*** We investigated clinical, endocrine and metabolic parameters in four family members carrying a novel IGF1R mutation (p.Tyr387X): an 18-year-old male (index case), his sister and two paternal aunts. ***Results:*** All family members showed a variable degree of impairment in prenatal growth, with birth weight standard deviation scores (SDS) between –1.65 and –2.37 and birth length SDS between –1.78 and –3.08. Their postnatal growth was also impaired, with height SDS between –1.75 and –4.86. The in-

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dex case presented high IGF-I levels during childhood and adolescence and delayed bone age. The index case and his two paternal aunts had impaired glucose tolerance (IGT) associated with a variable degree of alterations in insulin sensitivity and secretion. In contrast, the index case's sister, who had had IGT during pregnancy, showed normal glucose metabolism but reduced insulin sensitivity. ***Conclusion:*** This is the first study showing an association between a novel IGF1R mutation and a variable degree of alterations in prenatal and postnatal growth and in carbohydrate metabolism.

Introduction

Insulin-like growth factor-I (IGF-I) plays a key role in the regulation of intrauterine development, postnatal growth, cell proliferation, survival and bone growth [1, 2]. The biological effects of IGF-I are mediated through the type 1 IGF-I receptor (IGF1R) [3]. In recent years, several cases of heterozygous mutations in the *IGF1R* gene associated with prenatal growth retardation, small-for-gestational-age newborns and postnatal lack of catch-up growth despite sufficient IGF-I levels have been described [4–14]. In addition, other clinical characteristics reported in some but not all individuals with IGF1R mutations include bone retardation, microcephaly, modestly impaired mental development, dysmorphic features and delayed puberty [6, 12, 14, 15].

Growing evidence indicates a key role of the IGF-I/IGF1R system in regulating glucose metabolism by influencing β-cell function and insulin sensitivity [16, 17]. IGF-I has been shown to stimulate β-cell proliferation, and β-cell-specific knockout of the *Igf1r* gene in mice leads to defective insulin secretion [18, 19]. Several studies have also revealed that IGF-I can enhance peripheral insulin sensitivity [16, 20–22]. These insulin-like metabolic effects of IGF-I might be explained by its structural homology with the insulin molecule and by similarities between the insulin receptor and the IGF1R and the signaling cascades activated after hormone binding [3, 16]. However, despite these shared characteristics, genetic disturbances in the two genes lead to overlapping yet distinct phenotypes [3]. While there are well-described metabolic features associated with mutations in the insulin receptor, including mild to severe forms of insulin resistance, hyperinsulinemia, hyperglycemia and acanthosis nigricans, the few studies assessing glucose metabolism in young patients with IGF1R mutations could not demonstrate significant alterations [4, 5, 7]. However, the short follow-up of the reported cases could have limited the ability to detect abnormalities in glucose metabolism, which might not occur until adulthood.

Here we report on four adult members of an Italian family in whom a novel IGF1R mutation was associated with different degrees of impairment in prenatal and postnatal growth and in glucose metabolism.

Patients and Methods

Index Case and Family Members

The index case was an 18-year-old male who had been followed since childhood for severe short stature at the Department of Pediatrics, University of Chieti, Chieti, Italy. The other three family members were his older sister (27 years old) and two paternal aunts (a middle-aged aunt of 47 years and an older aunt of 50 years). All four family members provided written informed consent for all investigations. The study was approved by the Ethics Committee of the University of Chieti.

Height, weight, sitting height, head circumference and waist circumference were measured with standard equipment. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters, and body composition was assessed by single-frequency, phase-sensitive bioelectrical impedance analysis (Akern System Srl, Florence, Italy) [23]. Anthropometric standard deviation scores (SDS) were calculated [24].

Blood and serum samples were collected for DNA extraction and analysis of the *IGF1R* gene as well as for endocrine evaluation, respectively. In addition, all four family members underwent a standard oral glucose tolerance test (OGTT).

Genetic Analysis

Genomic DNA was extracted from peripheral leukocytes by standard procedures. All coding exons of the *IGF1R* gene were amplified by PCR using genomic DNA as template. PCR products were prescreened by a denaturing HPLC approach (WAVE, Transgenomic, Glasgow, UK) for the existence of any sequence inconsistency in comparison to a wild-type sample. Subsequently, PCR products showing conspicuous chromatograms were analyzed by dideoxy DNA sequencing.

Glucose Metabolism Assessment

All family members underwent a standard OGTT after a 10-hour overnight fast and were classified as having normal glucose tolerance, impaired glucose tolerance (IGT) or type 2 diabetes on the basis of the American Diabetes Association 2009 criteria [25]. Glucose and insulin levels were determined every 30 min for 2 h.

Indexes of insulin sensitivity and secretion were calculated. In particular, insulin sensitivity was determined by homeostatic model assessment of insulin resistance (HOMA-IR), calculated as (fasting insulin × fasting glucose)/22.5 [26], and by the whole-body insulin sensitivity index (WBISI), calculated as $10{,}000/\sqrt{[(\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean OGTT glucose} \times \text{mean OGTT insulin})]}$ [26]. β-Cell function was ascertained by HOMA-β, calculated as (fasting insulin × 20)/(fasting glucose – 3.5) [27],

Table 1. Anthropometric parameters

	Index case	Sister	Older paternal aunt	Middle-aged paternal aunt
Age, years	18	26	50	47
Birth weight, kg	2.6 (–2.03)	2.7 (–1.65)	2.6 (–1.89)	2.4 (–2.37)
Birth length, cm	45 (–3.08)	45 (–2.85)	47 (–1.78)	46 (–2.32)
Height, cm	143.9 (–4.86)	152.3 (–1.75)	146.2 (–2.78)	143.5 (–3.24)
Weight, kg	39	69	57.5	71
BMI	18.8	29.7	26.9	34.5
Waist circumference, cm	58.5	81	77	101.5
Fat mass, %	18	38	32	38
Lean mass, %	82	62	68	62
IGF-I, ng/ml[1]	435 [56.8] (+1.04)	265 [34.6] (+1.13)	127 [16.6] (–0.88)	106 [13.8] (+0.2)

Values in parentheses represent SDS. [1] Values in nanomoles per liter in square brackets.

and by the insulinogenic index, calculated from the OGTT data as Δinsulin (0–30 min)/Δglucose (0–30 min) [28].

Biochemical Assessments

Plasma glucose levels were determined with the glucose oxidase method (Sclavo, Siena, Italy), and plasma insulin was measured with a two-site immunoenzymometric assay (AIA-PACK IRI; Tosoh, Tokyo, Japan).

IGF-I and IGF-binding protein 3 were measured by immunoradiometric assay (Diagnostic Systems Laboratories Inc.) and converted to SDS based on normative data, as provided by the manufacturer.

Results

Index Case

The index case was a boy born at term as the second child of nonconsanguineous parents. His birth weight was 2.6 kg (SDS –2.03), and his birth length was 45 cm (SDS –3.08; table 1). Both parents were of short stature; the father's height was 155 cm (SDS –2.94) and the mother's height was 150 cm (SDS –2.14), resulting in a target height of 159 cm (SDS –2.4). The patient's father died at the age of 39 years due to acute leukemia.

Since early childhood, the patient showed impaired growth, for which he was evaluated for the first time at the age of 4 years (height 82 cm, SDS –4.58; fig. 1). He presented no dysmorphic features and his medical history was unremarkable, including normal early psychomotor development. At that time, celiac disease, hypothyroidism and other possible causes of growth retardation were excluded, whereas baseline IGF-I was high [159 ng/ml (20.8 nmol/l), SDS +2.6]. A clonidine stimulation test resulted

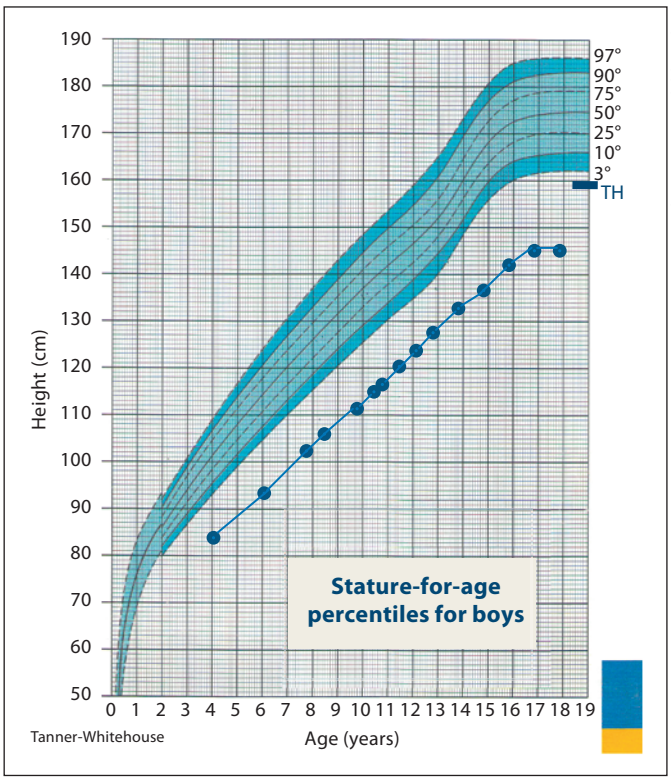

Fig. 1. Growth chart of the index case. TH = Target height.

in a normal growth hormone (GH) response (13.5 μg/l). At the age of 6 years, a second GH stimulation test was performed, confirming a normal GH response (18.8 μg/l). At that time, baseline IGF-I levels were still high [288 ng/ml (37.6 nmol/l), SDS +2.1], whereas IGF-binding protein

Table 2. Glucose metabolism data

	Index case (1st evaluation at 18 years)	Index case (2nd evaluation at 20 years)	Sister (26 years)	Older aunt (50 years)	Middle-aged aunt (47 years)
Metabolic variables					
Fasting glycemia, mmol/l	5.6	6.4	5.8	5.9	7.3
Two-hour glycemia, mmol/l	8.6	8.1	6.9	8.4	8.7
HbA1c, %	4.9	–	5.8	5.7	5.5
Insulin sensitivity indexes					
HOMA-IR	3.24	1.74	4.17	2.36	4.54
WBISI	2.19	3.39	3.29	3.93	2.79
β-Cell function indexes					
Fasting insulin, pmol/l	90.3	42.4	118.8	62.5	97.2
Two-hour insulin, pmol/l	1,145.9	664.6	572.3	463.9	393.1
C-peptide, nmol/l	1.07	0.73	1.90	0.67	1.26
Two-hour C-peptide, nmol/l	–	4.03	3.43	2.73	3.06
HOMA-β	123	42	140	76	74
Insulinogenic index	22	23	16	2.4	2.1

3 was normal for his age and sex (182 nmol/l). Given his severe short stature and reduced growth rate, at the age of 8 years a course of GH therapy [recombinant human GH (rhGH); dose 0.26 mg/kg/week] was tried and continued for 1 year without any improvement in his growth velocity, which remained in his original growth channel. According to the Greulich-Pyle method, his bone age, assessed at a chronological age of 9.7 years, was delayed by 1.7 years.

Due to the persistence of impaired growth, at the age of 12 years another GH stimulation test was performed, during which GH rose from 3.9 to 16.4 μg/l, and high baseline IGF-I levels were confirmed [469 ng/ml (61.3 nmol/l), SDS +2.3].

Pubertal development started at the age of 12 years and progressed normally, although the boy did not present any pubertal spurt, resulting in a short proportionate final height of 143.9 cm (SDS –4.86; upper to lower body ratio 0.97) achieved at the age of 18 years (table 1; fig. 1). At this time, he was a normal weight with a BMI of 18.8, and his head circumference was 54.2 cm (SDS –1.7).

IGF-I levels remained markedly elevated for his age, sex and pubertal development during the whole period of growth and continued to be elevated into late adolescence [at 17 years: 585 ng/ml (76.5 nmol/l), SDS +2.5], with a subsequent decline [at 18 years: 435 ng/ml (56.8 nmol/l), SDS +1.04; at 20 years: 329 ng/ml (43 nmol/l), SDS +0.08].

At the age of 18 years, a genetic analysis was performed, revealing a heterozygous mutation in the *IGF1R* gene. At that time, the patient also underwent an OGTT (table 2), which showed IGT (8.6 mmol/l) associated with normal fasting glucose levels (5.6 mmol/l). HOMA-IR was slightly elevated (3.24), while WBISI was low (2.19), indicating a mild degree of insulin resistance, whereas both basal (HOMA-β 123.2) and stimulated insulin secretion (insulinogenic index 22) were normal. After 2 years, a second OGTT was performed, confirming IGT in the presence of raised fasting glucose levels (6.4 mmol/l). This was associated with lower basal insulin levels leading to markedly reduced HOMA-β. In contrast, stimulated insulin secretion was maintained (table 2).

Sister

The patient's sister was born at term after an uneventful pregnancy with a weight of 2.7 kg (SDS –1.65) and a length of 45 cm (SDS –2.85; table 1). Her physical and neurological development were normal, and there were no remarkable findings in her medical history. Menarche occurred at the age of 12 years. She was evaluated at the age of 27 years, when her height was in the lower part of the normal range (height 152.3 cm, SDS –1.75) and she was overweight, with a BMI of 29.7. Her plasma IGF-I was in the upper part of the normal range for her sex and age on two occasions [IGF-I 265 ng/ml (34.6 nmol/l), SDS +1.13].

An OGTT performed at the age of 27 years revealed normal glucose tolerance, with fasting and 2-hour glucose of 5.8 and 6.9 mmol/l, respectively. Insulin levels as well as HbA1c were normal (table 2). HOMA-IR was high, and WBISI was slightly reduced, indicating insulin resis-

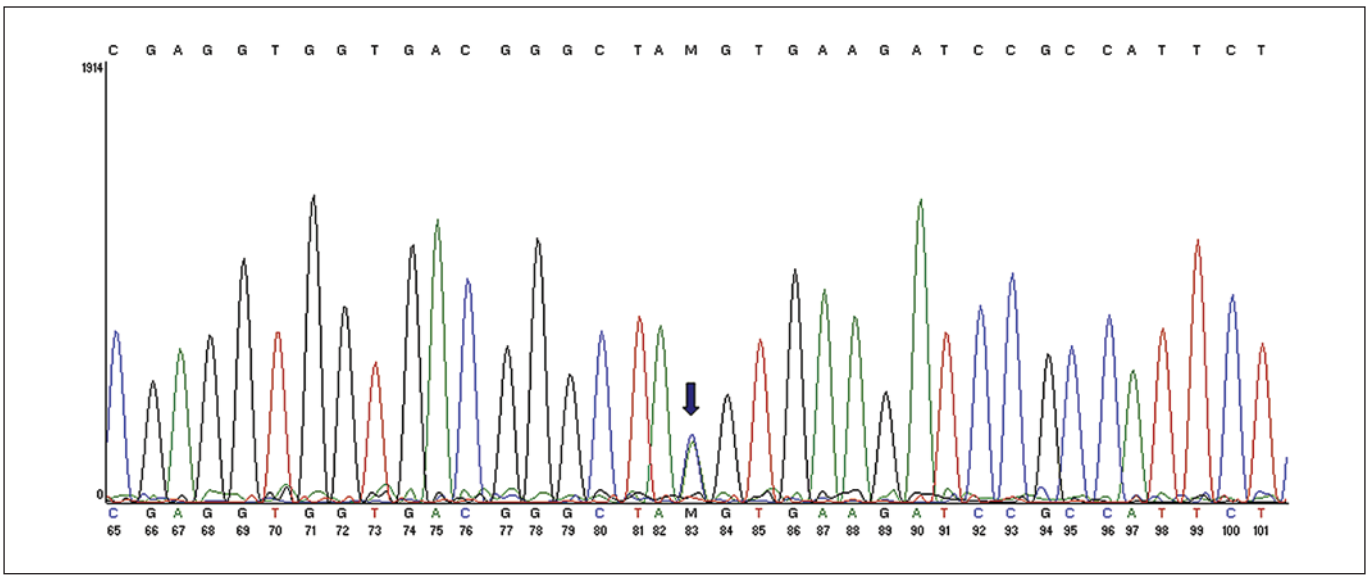

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Fig. 2. Sequence analysis of *IGF1R* cDNA of the family.

tance. Basal and stimulated insulin secretion were normal (table 2). A second OGTT was performed after 2 years, confirming normal glucose tolerance (data not shown). During her first and only pregnancy she developed IGT.

Older Paternal Aunt

The older paternal aunt was born at term after an uncomplicated pregnancy with a birth weight of 2.6 kg (SDS –1.89) and a birth length of 47 cm (SDS –1.78; table 1). She reported stunted growth and normal neurological development. Menarche had occurred at the age of 14 years and menopause at the age of 47 years. Anthropometric measurements obtained at the age of 50 years revealed a reduced final height of 146.2 cm (SDS –2.78) and a BMI of 26.9. IGF-I was in the normal range for her sex and age [127 ng/ml (16.6 nmol/l), SDS –0.88].

At that time, an OGTT was performed, which showed IGT (8.4 mmol/l) associated with normal basal insulin secretion (HOMA-β 75.6), whereas her stimulated insulin secretion was markedly reduced (insulinogenic index 2.4; table 2).

Middle-Aged Paternal Aunt

The middle-aged paternal aunt was born after an uneventful pregnancy with a birth weight of 2.4 kg (SDS –2.37) and a birth length of 46 cm (SDS –2.32; table 1). She had stunted growth with normal neurological development. Menarche had occurred at the age of 12 years and menopause at the age of 45 years. She was assessed at the age of 47 years, when she presented with severe short stature (height 143.5 cm, SDS –3.24) associated with normal IGF-I levels [106 ng/ml (13.8 nmol/l), SDS +0.2]. She was frankly obese with a BMI of 34.5.

At that time, glucose metabolism assessment showed impaired fasting glucose and IGT, with fasting and 2-hour glucose of 7.3 and 8.7 mmol/l, respectively. HOMA-IR was high, and WBISI was low, indicating reduced insulin sensitivity. This was associated with reduced β-cell function, as indicated by low values of the insulinogenic index and HOMA-β (table 2).

Genetic Analysis

Sequence analysis of the *IGF1R* PCR fragments obtained from genomic DNA revealed a heterozygous C to A substitution within exon 5 (c.1161C>A) that alters the coding nucleotide triplet from TAC to TAA (fig. 2). The introduction of this nonsense mutation is predicted to result in premature peptide chain termination at tyrosine 387 (p.Tyr387X) within the full-length IGF1R. The deduced heavily truncated receptor would lack the fibronectin domains of the α-subunit as well as the entire β-subunit, leading to loss of plasma membrane anchorage. However, introduction of a premature termination codon frequently results in nonsense-mediated decay, a cellular mechanism that prevents the translation of potentially

toxic peptides encoded by a premature termination codon carrying aberrant mRNAs [5].

This mutation was present in all four family members described here, whereas it was not found in the index case's mother. Therefore, the mutation is likely to have been inherited from the father (who was already deceased at the time of evaluation), because the two paternal aunts were shown to harbor the same mutation.

Discussion

This report presents four members of a family with different degrees of prenatal growth retardation and short stature bearing the same heterozygous mutation in the *IGF1R* gene.

Different types of mutations in the *IGF1R* gene have been described previously and have been clearly linked with impaired intrauterine growth and short stature [4–14]. However, carriers of the mutations demonstrated variable degrees of growth retardation, probably explained by the action of modifier genes in the genetic background. In our family, despite detecting the same mutation in all four members, the intrafamilial variability in terms of compromised intrauterine and postnatal growth was particularly apparent. Specifically, the index case was affected by prenatal growth failure, characterized by low birth weight and length, and impaired postnatal growth leading to severe short stature. These prenatal and postnatal growth characteristics were similar in his middle-aged paternal aunt. In contrast, his sister and older aunt had low to normal birth weights. Their final heights were below average but not of the same severity as the other two family members. Borderline growth retardation at birth was already described for index cases in two previous reports [10, 12]. Similarly, although none of the cases with IGF1R mutations reported so far showed postnatal catch-up growth, a different degree of impairment in final height was observed [4–14]. This could result from the interaction of the IGF1R defect with other genetic and/or environmental factors. In addition, a potential variation in the expressivity of the same mutation might explain the variable phenotype within a family.

Bone age was delayed in our index case, similarly to the majority of other cases reported in the literature [4–14]. In contrast, neither our index case nor any of the other family members presented any of the dysmorphic features previously associated with some IGF1R mutations [4, 6, 14].

The developmental milestones of our index case during childhood were normal, although his school performance was slightly impaired and as a young adult he reported occupational difficulties. This could suggest a degree of impairment in his cognitive function. Psychomotor problems have been reported in some individuals with IGF1R mutations and could be explained by the known effect of the GH-IGF-I components on brain development and function [29].

Persistently high IGF-I levels were detected in our patient throughout childhood and adolescence, with normalization in late adolescence and early adulthood. Slightly increased IGF-I levels were also found in his sister, whereas the other two adult family members had normal concentrations. Levels of IGF-I have been reported to be normal or high in patients with heterozygous IGF1R mutations and reflect a status of IGF-I resistance, which was also confirmed by the lack of response to a standard dose of rhGH in our index case. In line with this latter observation, a variable response to exogenous GH has been reported previously, with benefits mainly associated with longer-term treatment or with higher doses of rhGH [5, 7, 13].

No functional assessment of the IGF1R mutation was possible for this family, although many of the characteristics we found in the four members were similar to those previously reported in carriers of other terminal IGF1R mutations [4, 5]. The nonsense terminal mutation likely leads to a nonfunctional IGF1R lacking its membrane anchorage. However, as recently reported for other cases of IGF1R mutations [5], the involvement of the nonsense-mediated decay pathways and the consequent degradation of the *IGF1R* mRNA expressed from the mutant allele, leading to IGF1R haploinsufficiency, cannot be excluded.

The diversity in the observed growth phenotypes in the four family members was associated with a different degree of alteration in glucose metabolism. Normal glucose homeostasis is highly dependent on the well-known interplay between β-cell function and insulin sensitivity [30]. In this respect, in recent years genetic variants of components of the IGF system have been suggested as potential factors implicated in the multifactorial pathogenesis of type 2 diabetes [31, 32]. In line with this, the alterations in glucose metabolism we found in our family members and which were suggestive of type 2 diabetes might reflect the lack of IGF-I modulation of β-cell function and insulin sensitivity. Until now, abnormalities in glucose metabolism have not been investigated or, where assessed, not found in young patients with IGF1R muta-

tions, probably due to the short period of follow-up of these cases [5, 7]. In contrast, a mild degree of insulin resistance was detected in a 35-year-old patient carrying an IGF1R mutation [6].

To the best of our knowledge, this is the first family pedigree with ages ranging from young to advanced adulthood where, interestingly, carriers of the same heterozygous mutation in IGF1R also presented different degrees of alterations in carbohydrate homeostasis.

Even as a normal-weight young adult, the index case presented IGT with rising fasting glycemia over a 2-year observational period, suggesting the potential role of inherited factors. The middle-aged obese aunt had impaired fasting glucose, whereas the older overweight aunt exhibited normal fasting glycemia in the presence of IGT. The obese sister did not show any alteration in carbohydrate homeostasis, but she had developed transient IGT during a previous pregnancy. These different degrees of glucose intolerance were associated with a variable combination of alterations in β-cell function and insulin sensitivity, which might be related, at least in part, to the overweight/obesity status of some of the family members.

Although based on clinical observations, the described alterations in carbohydrate homeostasis in family members bearing an IGF1R mutation suggest that alterations of the IGF-I/IGF1R components might interfere with glucose metabolism, although the exact mechanism remains to be ascertained. There is evidence suggesting an association between being born small for gestational age, as all our family members were, and reduced β-cell function [33], and this appears to be related to hormonal imbalances during intrauterine life [34], including potential alterations in the IGF-I/IGF1R system. In addition, IGF-I appears to be involved in the regulation of β-cell function during postnatal life, particularly in the presence of stimuli requiring increased insulin production, as suggested by experimental studies [17]. The association between IGF-I and type 2 diabetes is also supported by the observation that a polymorphism in the promoter region of IGF-I was associated with type 2 diabetes [31], although the link between genetic variants in IGF-I/IGF1R and insulin secretion was not confirmed in a Danish study [35]. However, these contrasting results suggest the need for further genetic studies in larger populations to clarify this issue. Besides, the well-known and tissue-specific direct effects of IGF-I on insulin action should not be underestimated [20, 36], particularly in our lean index case, who developed IGT at a young age, associated with reduced insulin sensitivity and, only later on, reduced β-cell function.

Further studies are required to better explore our clinical observations and to assess whether there is a true causal relationship between IGF1R mutations and IGT.

In summary, the present study reports a novel mutation in the IGF1R in four family members associated with a variable degree of prenatal and postnatal growth impairment. In addition, the four family members presented alterations in carbohydrate metabolism, consisting of a variable phenotype ranging from normal glucose tolerance in the presence of insulin resistance to IGT and fasting hyperglycemia in association with both insulin resistance and impaired β-cell function, suggesting a potential interaction between altered IGF-I signaling and glucose homeostasis.

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