A novel heterozygous IGF-1 receptor mutation associated with hypoglycemia

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Abstract
Mutation in the insulin-like growth factor-1 receptor (IGF1R) gene is a rare cause for intrauterine and postnatal growth disorders. Patients identified with IGF1R mutations present with either normal or impaired glucose tolerance. None of the cases described so far showed hypoglycemia. We aimed to identify the genetic basis for small for gestational age, short stature and hypoglycemia over three generations in one family. The proband, a 9-year-old male, presented in infancy with recurrent hypoglycemic episodes, symmetric intrauterine growth retardation and postnatal growth retardation. Blood DNA samples from the patient, his parents, a maternal sister and maternal grandmother underwent Sanger sequencing of the IGF1R gene. Primary skin fibroblast cultures of the patient, his mother and age- and sex-matched control donors were used for gene expression and receptor functional analyses. We found a novel heterozygous mutation (c.94+1g→a, D1105E) affecting the splicing site of the IGF1R mRNA in the patient, his mother and his grandmother. Primary fibroblast cultures derived from the patient and his mother showed reduced proliferation and impaired activation of the IGF1R, evident by reduced IGF1R and AKT phosphorylation upon ligand binding. In conclusion, the newly identified heterozygous missense mutation in exon 1 of IGF1R (D1105E) results in impaired IGF1R function and is associated with small for gestational age, microcephaly and abnormal glucose metabolism. Further studies are required to understand the mechanisms by which this mutation leads to hypoglycemia.

Introduction
Growth retardation in children is multifactorial. While most conditions associated with growth impairment are amenable to genetic and molecular analyses, a significant portion of the cases is classified as idiopathic because no specific (genetic or other) defect can be recognized. Growth and developmental conditions under the umbrella of...
**IGF1R mutation with SGA and hypoglycemia**

**Patients and methods**

**Index case and family members**

The index case was referred for endocrine evaluation at the age of 7 months due to episodes of hypoglycemia. Blood samples were obtained from the patient's father, mother, maternal aunt and maternal grandmother. Height was determined with Harpenden stadiometer, and weight and head 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. Bone age was evaluated by the method of Greulich and Pyle (22). The study was approved by the Rabin Medical Center Ethics Committee, Israel, and the parents gave informed consent for the studies. Plasma GH was measured by a solid-phase two-site chemiluminescent immunometric assay (Immulite 2000; Siemens). Plasma IGF-1 was determined using a one-step sandwich chemiluminescence immunoassay (DiaSorin, Saluggia, Italy). Blood samples were collected for DNA extraction. Skin biopsies from the proband and his mother as well as age- and sex-matched controls provided skin fibroblasts for analysis.

**Sanger sequencing**

The determination of the IGF1R gene (ENST00000268035, NM_000875.3) mutation was performed on DNA extracted from whole blood and screened using forward and reverse primers (available upon request to the authors) flanking all 21 coding and splicing exons regions. Detection was done by Sanger sequencing, loaded on an ABI 16 capillary apparatus (23).

**Cell cultures and treatments**

The skin fibroblasts were grown in Chang Medium (BIOAMF-1 basal medium, Biological Industries Ltd., Beit HaEmek, Israel), supplemented with glutamine and antibiotics (penicillin/streptomycin/nystatin). Cells were treated with 50 ng/mL of IGF-1 (CytoLab, Rehovot, Israel). Stock concentration of IGF-1 was 1 mg/mL.

**Real-time quantitative polymerase chain reactions (RQ-PCR)**

Total RNA was prepared from fibroblast cultures using TRIzol (Life Technologies). Single-stranded cDNA was synthesized from total RNA samples using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems). IGF1R mRNA levels were measured by RQ-PCR, using the following primers: sense 5’-GAAGTGGAACCCTCCCTCTC-3’; antisense 3’-GAATGGAACCCCTCCCTCTC-5’.
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Western immunoblots

Cells were washed with ice-cold phosphate-buffered saline containing 5 mM EDTA and lysed in a buffer composed of 150 mM NaCl, 20 mM Hepes, pH 7.5, 1% Triton X-100, 2 mM EGTA, 1 mM PMSF, 2 µg/mL aprotinin, 1 mM leupeptin, 1 mM pyrophosphate, 1 mM vanadate and 1 mM DTT. Protein extracts (50 µg protein) were subjected to 10% SDS-PAGE and transferred to nitrocellulose membranes. Membranes were blocked with 5% non-fat milk in T-TBS (20 mM Tris–HCl, pH 7.5, 135 mM NaCl and 0.1% Tween20) and then incubated with antibodies against total- and phospho-IGF1R (# SC-3027 and SC-3024, Santa Cruz Biotechnology), total- and phospho-ERK (# SC-9102 and SC-9106, Santa Cruz Biotechnology) and total- and phospho-AKT (# SC-9272 and SC-9271, Santa Cruz Biotechnology). Proteins were detected using the SuperSignal West Pico chemiluminescent substrate (Pierce).

XTT cell proliferation assay

Cell proliferation was monitored using an XTT cell proliferation kit (Biological Industries Ltd) according to the manufacturer’s instructions. Fibroblasts were seeded at a density of 7000 cells/well in 96-well plates. Proliferation rate was measured 24 h following seeding.

Statistical analyses

The statistical significance of differences between groups in proliferation assays was assessed by the Student’s t-test (two samples, equal variance). P values <0.05 were considered statistically significant.

Results

Clinical presentation of the patient

The patient was born at 36 weeks of gestation as the second child of non-consanguineous parents of Ashkenazi Jewish origin (Fig. 1). His birth weight was 1875 g (~2.5 SDS); birth length was not documented. At 7 months of age, he was referred for endocrine evaluation due to episodes of hypoglycemia. He had a documented episode of hypoglycemia on the second day of life, with no further episodes at the neonatal care unit. The patient suffered from severe gastro-esophageal reflux and poor appetite due to delayed gastric emptying. At 7 months of age, during an episode of continuous vomiting, he had documented hypoglycemia of 31 mg% (1.7 mmol/L). When admitted, his weight was 4.59 kg (~4.9 SDS), length was 60.5 cm (~3.2 SDS), head circumference was 41 cm (~2.5 SDS) and bone age that of a newborn. Clinodactyly, micrognathia and high-arched palate were also detected. His overall developmental milestones have been appropriate, his school performance (at age 9 years) is excellent and he participates in a program for gifted children.

The metabolic profile, including liver function tests, ammonia, lactate, pyruvate, free fatty acids, acetoacetate and beta-hydroxybutyrate, was normal. Samples drawn during several episodes of hypoglycemia showed undetectable levels of insulin and low C-peptide levels. Peak ACTH-stimulated cortisol was 795 nmol/L (normal ≥500 nmol/L). The patient and his parents do not carry either of the 2 ABCC mutations commonly associated with hyperinsulinism of infancy in Ashkenazi Jews (24). Basal IGF-1 levels were within the normal range for age: 64 and 72 ng/mL (range 33–102). However, arginine- or glucagon-stimulated GH concentrations were subnormal: 4.1 ng/mL and 7.6 ng/mL, respectively (~10.0 ng/mL considered a normal response).

Brain MRI revealed normal morphology of hypothalamus, stalk and hypophysis. Treatment with recombinant human GH (rhGH, 50 µg/kg/day) was
initiated at 1 year of age, increasing the length-SDS from −3.2 to −2.1 SDS after 1 year and to −1.5 after 2 years. His current height −SDS is −0.65, and the upper/lower ratio is 1.01. Medical concern following diagnosis of colonic polyps led to discontinuation of GH therapy at 8 years of age. IGF-1 was increased during therapy, with values ranging from +1.5 to +2.4 SDS for age and gender and remained increased at +1.97 SDS while off therapy (Fig. 2).

Following the hypoglycemic episode at 7 months of age, there were no clinical or documented hypoglycemic events until 2 years of age, when symptomatic hypoglycemic events, both fasting and postprandial, occurred. Hypoglycemic episodes occurred almost every day and were not necessarily related to vomiting or intercurrent illness, although they were more frequent when intervals between meals were longer. Glucose levels ranged between 19 and 60 mg%, as documented by glucose meter, laboratory analysis on several occasions and by the continuous glucose monitoring system. Fast tests performed twice added no further information. The hypoglycemic events occurred day and night and persisted despite frequent feedings with carbohydrate-enriched meals and Proglycem (diazoxide) treatment.

A percutaneous feeding gastrostomy was also inserted as the gastro-esophageal reflux was associated with daily vomiting leading to hypoglycemic episodes and poor weight gain. The hypoglycemic episodes lessened significantly following insertion of a feeding gastrostomy as well as installation of a continuous glucose monitoring device, which by warning of a potential low glucose event can prevent or reduce the severity of hypoglycemia. Cessation of GH treatment notably had no effect on the hypoglycemic episodes.

Rectal bleeding at the age of 7.5 years was associated with benign polyps at the terminal ileum and at the cecum, showing normal mucosa and lymphoid hyperplasia on histopathology. Clinical characteristics of the three affected family members are shown in Table 1.

The patient’s mother was born with a birth weight of 1100 g (−4.3 SDS) at 40 weeks of gestation. Her menarche occurred at 14 years of age. A hypoglycemic episode was first documented at the age of 18 years, but she recalled having similar episodes during childhood. The onset of hypoglycemic events was not associated with change of eating habits, physical activity or any medications. Upon her first visit to our clinic with the patient, the mother was 32 years of age with a height of 154 cm (−1.6 SDS), BMI 18.6 kg/m² and head circumference of 49 cm (−5.0 SDS). The mother is a bright woman who graduated from law school. She reported excision of two benign colonic polyps diagnosed following rectal bleeding.

The mother presented with normal peak ACTH-stimulated cortisol, thyroid function and normal anterior hypophysis hormones (prolactin, TSH, LH, FSH). An oral glucose tolerance test revealed normal glucose tolerance with a relatively high insulin and C-peptide response (Table 2). Serum IGF-1 levels were elevated in two of three samples drawn on different occasions. The mother still suffers from hypoglycemic episodes, as documented during a recent hospitalization and by a continuous glucose monitoring system. The glucose meter showed levels as low as 44 mg%, verified by laboratory analysis. Two hours after fast test initiation hypoglycemia of

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**Table 1** Clinical characteristics of the affected patients with a heterozygous IGF1R mutation.

<table>
<thead>
<tr>
<th></th>
<th>Index case</th>
<th>Mother</th>
<th>Grandmother</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>9</td>
<td>40</td>
<td>71</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Birth weight (g) (SDS)</strong></td>
<td>1875 (−2.5)</td>
<td>1100 (−6.4)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Height at evaluation (cm)</strong></td>
<td>60.5 (−3.2)</td>
<td>154 (−1.6)</td>
<td>154 (−1.6)</td>
</tr>
<tr>
<td><strong>Current head circumference (cm)</strong></td>
<td>49 (−2.6)</td>
<td>49 (−5.0)</td>
<td>49 (−5.0)</td>
</tr>
<tr>
<td><strong>Current BMI (kg/m²)</strong></td>
<td>14.3 (−1.15)</td>
<td>18.6 (−1.9)</td>
<td>25.7 (0.8)</td>
</tr>
<tr>
<td><strong>Hypoglycemic events</strong></td>
<td>Documented</td>
<td>Documented</td>
<td>Reported</td>
</tr>
<tr>
<td><strong>Peak cortisol (nmol/L)</strong></td>
<td>795</td>
<td>596</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
<td>Colonic polyps</td>
<td>Colonic polyps</td>
<td>None</td>
</tr>
<tr>
<td><strong>Neurocognitive function</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

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**Figure 2**
Serum IGF-1 levels of the index case, expressed as SDS for age and gender.
31 mg% occurred, with insulin of 40.1 pmol/L. Work-up for insulinoma, including imaging, was negative.

The father of the patient is healthy, 181 cm tall (+0.8 SDS), BMI 29.6 kg/m². The birth weight of the patient’s brother was 2800 g and length, 51 cm. His current height (at 13 years) is −0.8 SDS and weight −0.09 SDS. SGA and relatively short stature were noted in several other maternal family members, including the maternal grandmother (Fig. 1, II 8). At age 71 years, her height was 154 cm (−1.6 SDS), BMI 25.4 kg/m² and head circumference 49 cm (−5.0 SDS). Menarche occurred at age 14.5 years. Episodes of weakness and tremor when she was younger had resolved following a sweet drink and may have resulted from hypoglycemia. At age 50 years, she was diagnosed with type 2 diabetes and is currently treated with insulin. Her mother and three of her siblings suffered from diabetes; two of them (II1, II7) are reported to have had hypoglycemic events at a young age. The clinical features of SGA, poor appetite and poor feeding, delayed gastric emptying, prominent forehead, clinodactyly and recurrent hypoglycemia could be compatible with Russell-Silver syndrome (24). However, analysis for the common mutations of Russell-Silver was negative.

**Molecular analysis**

Molecular evaluation of the *IGF1R* gene revealed a novel heterozygous c.94 +1g>, a mutation affecting splicing of the mRNA. The mother and maternal grandmother are carriers of the same mutation. The maternal aunt and the unaffected father do not carry the mutation. The mutation was not found in large population databases, such as ExAC and ESP, or in 380 alleles in our internal database. mRNA analysis showed that this sequence change causes an addition of four nucleotides at the end of exon 1 and, as a result, frameshift and truncation of the protein – p.I32NfsX114. Owing to the location of the mutation at exon 1, using an *in silico* model of the mutated protein was impossible.

**Functional studies**

To evaluate the impact of the identified *IGF1R* mutation on IGF1R function, we isolated skin fibroblasts from the patient and his mother as well as from age/sex-matched control subjects. Primary fibroblast cultures were serum starved for 24 h, after which they were treated with IGF-1 (50 ng/mL) for 10 min. At the end of the incubation period, phosphorylation of the IGF1R, extracellular signal-regulated kinase 1/2 (ERK1/2) and protein kinase B/AKT were measured by Western immunoblotting. As expected, while addition of IGF-1 resulted in significant IGF1R phosphorylation in control cells (Fig. 3), IGF1R phosphorylation was absent in the patient’s fibroblasts and was very low in protein extracts from the patient’s mother. Lack of IGF1R phosphorylation may result from haploinsufficiency of the IGF1R gene or, alternatively, low sensitivity of the Western immunoblot with a specific phospho-IGF1R antibody. Likewise, IGF-1 induced phosphorylation of AKT in fibroblasts from the patient’s mother, but not in control cells. Addition of IGF-1 had no further effect on ERK phosphorylation in the patient cells, suggesting that the protein was already maximally activated under basal conditions.

### Table 2  Biochemical evaluation of the mother with a heterozygous IGF1R mutation.

<table>
<thead>
<tr>
<th></th>
<th>Glucose (mmol/L)</th>
<th>C-peptide (pmol/L)</th>
<th>Insulin (mmol/L)</th>
<th>GH (ng/mL)</th>
<th>IGF-1 (ng/mL)</th>
<th>HbA1c % (mmol/L)</th>
</tr>
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<tbody>
<tr>
<td>Normal range</td>
<td></td>
<td>0.3–2.4</td>
<td></td>
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<td></td>
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<tr>
<td>OGTT at 32 years</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>0′</td>
<td>87</td>
<td>0.56</td>
<td>75</td>
<td></td>
<td>153–322</td>
<td>4.2–5.7</td>
</tr>
<tr>
<td>1 h</td>
<td>129</td>
<td>2.19</td>
<td>382</td>
<td></td>
<td></td>
<td>5.1 (32)</td>
</tr>
<tr>
<td>2 h</td>
<td>105</td>
<td>&gt;2.32</td>
<td>451</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3 h</td>
<td>89</td>
<td>2.23</td>
<td>375</td>
<td></td>
<td></td>
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<tr>
<td>OGTT at 37 years</td>
<td></td>
<td></td>
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<tr>
<td>0′</td>
<td>81</td>
<td>0.36</td>
<td>41.5</td>
<td></td>
<td>8.63</td>
<td>270.4</td>
</tr>
<tr>
<td>1 h</td>
<td>153</td>
<td>2.38</td>
<td>345</td>
<td></td>
<td></td>
<td>5.4 (36)</td>
</tr>
<tr>
<td>2 h</td>
<td>131</td>
<td>2.67</td>
<td>257</td>
<td></td>
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<tr>
<td>Fast test at 40 years</td>
<td></td>
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<tr>
<td>0′</td>
<td>64</td>
<td>0.37</td>
<td>40.1</td>
<td></td>
<td></td>
<td>5.1 (32)</td>
</tr>
<tr>
<td>120′</td>
<td>31</td>
<td></td>
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<tr>
<td>Random blood samples</td>
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<tr>
<td>At 33 years</td>
<td>70</td>
<td>0.35</td>
<td>142</td>
<td>0.43</td>
<td>472.5</td>
<td>358.5</td>
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<tr>
<td>At 39 years</td>
<td>80</td>
<td></td>
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</table>
Proliferation assays

To assess the impact of the IGF1R mutation on cell proliferation, XTT assays were used. Fibroblasts were grown in serum-containing media for 24h, after which proliferation tests were performed. As shown in Fig. 4, marked differences were seen between mother and proband and control cells. Specifically, the proliferation rate of the mother's cells was reduced by 60% compared to that of control cells, whereas that of the child was reduced by 40% (P<0.05). Similar reductions in proliferation rates of the cells of the patient and of the mother as compared to those of healthy fibroblasts were seen when using a H3-thymidine incorporation protocol (data not shown). Taken together, these data suggest a direct link between lack of IGF1R activation and impaired proliferation.

Discussion

We report the identification of a novel heterozygous IGF1R mutation (c.94+1g>a) in three microcephalic and relatively short-statured members of the same family, presenting with hypoglycemia early in life. The development of subsequent impaired glucose tolerance and diabetes later in life may be attributed to the same mutation. While most clinical features of the affected family members across three generations were similar to those of patients with IGF1R mutations previously described (1, 21), including SGA, microcephaly and relatively short stature, this is, to the best of our knowledge, the first report of an IGF1R gene mutation manifesting with hypoglycemia. Indeed, previously described IGF1R mutations were either associated with impaired glucose metabolism (3, 14, 15, 16, 25, 26) or had no effect on glucose metabolism (2, 5, 6, 7, 9, 10, 12, 13, 20). To date, only one girl with a deletion on 15q26.2, resulting in a single IGF1R gene copy, has been reported as having recurrent hypoglycemic episodes (26). The authors, however, could not explain the etiology of this condition. Hypoglycemia has not been reported in other patients with 15q26.3 deletion (16, 19, 20).

Children who are hemizygous at the IGF1R locus usually show growth failure (1, 21), and some craniofacial abnormalities, including microcephaly, triangular facies, hypertelorism, high-arched palate, abnormal ears and micrognathia, as well as skeletal abnormalities including...
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Hypoglycemic episodes occurred in the grandmother and two of her siblings in their twenties, in the mother during childhood and in our patient during infancy. This could constitute a typical case of genetic anticipation. Several mechanisms may have contributed to the hypoglycemic events. These mechanisms include the following: (1) Increased insulin sensitivity. Classical haploinsufficiency of IGF1R due to loss of about half the receptor concentration was shown to improve the insulin sensitivity in the patient’s fibroblasts, as demonstrated by a quantitative increase of AKT activation in response to insulin (9). (2) The paucity of IGF-1 receptors could result in a high content of hybrid receptors, composed of one α/β IGF1R hemireceptor linked to one α/β insulin receptor hemireceptor. Hybrid receptors containing the IR-B isoform are expressed predominantly in muscle and adipose tissue (29), which are important target tissues for insulin action. A recent laboratory study suggested that binding of IGF-1 to this particular hybrid receptor may be as potent in stimulating glucose uptake as insulin binding to its cognate receptor (30). (3) Laboratory studies have shown that IGF-1 can promote glucose uptake in certain peripheral tissues (31). Although the magnitude of this effect is only 4–7% of that of insulin (32), the molar concentration of IGF-1 in human plasma is 100-fold greater than that of insulin. This difference in concentrations is further accentuated in our patients. (4) IGF-1 can suppress hepatic glucose production (33, 34, 35). Despite a low number of receptors, high IGF-1 values may have a compensatory effect, leading to hypoglycemia. (5) The high IGF-1 levels may have suppressed GH and blunted its glycemic effect. This hypothesis is supported by the finding of subnormal GH levels in our patient, but should be questioned as GH therapy did not seem to ameliorate hypoglycemic episodes. (6) High circulating IGF-1 could bind to the insulin receptor, as insulin and IGF-1 are known to bind to each other’s receptors (albeit with low affinity and, usually, at supra-physiological levels) (36, 37). The first two options, suggesting increased insulin sensitivity, are more likely, while the rest are associated with increased IGF-1 level, not found initially in our patient. The question which of these (or other) putative mechanisms led to hypoglycemia in our patient, and not in patients with other IGF1R mutations described to date, remains to be elucidated.

It is possible that the diabetes that developed later in life in the grandmother, who carries the mutation, and in at least two of her brothers might be associated with the mutation. The evolution of the disorder from hypoglycemia to overt diabetes is very complex, and the pathogenic mechanism may involve both β-cell exhaustion and apoptosis. There is some genetic evidence for a role of IGF-1 in glucose metabolism. In particular, a rare state of IGF-1 deficiency related to a homozygous partial deletion in the IGFI gene (IGF1) has been associated with severe insulin resistance, which was normalized by IGF-1 therapy (38). IGF-1 resistance due to the mutation could block this effect and induce insulin resistance, which over a long period of time may lead to β-cell exhaustion. β-cells express the IGF1R, and the tyrosine kinase activity of these receptors could potentially alter insulin secretion by influencing cell replication and survival (39, 40). Moreover, as IGF-1 has a positive anti-apoptotic effect (41), resistance may contribute to β-cell apoptosis. Furthermore, as insulin resistance worsens and insulin levels rise, these higher insulin levels result in lower serum IGFBP-1 levels, upregulation of hepatic IGF-1 production and higher levels of free (presumably, bioactive) IGF-1 levels.

The subnormal response of GH to stimulation in the index case may represent transient GH deficiency rather than true deficiency. It is well recognized, based on multiple studies that in the majority of patients diagnosed as idiopathic GH deficiency, this proves to be transient when re-evaluated at final height. This is especially true in partial GH deficiency, as was the case in our patient. As other pituitary hormonal axes were intact, brain MRI normal and stimulated GH consistent with partial GH deficiency (peak GH 7.6 ng/mL), this may be a case of transient GH deficiency. At one year of age, when he presented with hypoglycemia, GH response was subnormal and length was −3.3 SD and therapy was clinically required. Growth significantly improved following therapy initiation. However, it is impossible to determine if it was GH effect or simply catch-up growth of an SGA infant. Hypoglycemic episodes were not affected by GH therapy or its cessation, indicating that its role in the pathogenesis of hypoglycemia, if at all, was minor.
Conclusion

We report on a new heterozygous missense mutation in exon 1 of IGFIR in three generations presenting with SGA, microcephaly and hypoglycemia. This mutation affects the splicing of the mRNA transcript, leading to addition of four nucleotides at the end of exon 1. The net result of this frameshift mutation is a truncation of the receptor protein. It is reasonable to assume that this genetic lesion leads to a reduction in IGFI binding. In turn, the mutation leads to decreased IGF1R phosphorylation and variable downstream response. Furthermore, IGFIR mutation was associated with a decreased proliferation rate. The molecular and biochemical events leading to hypoglycemia are yet to be elucidated.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Acknowledgement
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