

BRIEF REPORT

Paternally Inherited *IGF2* Mutation and Growth Restriction

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SUMMARY

In humans, mutations in *IGF1* or *IGF1R* cause intrauterine and postnatal growth restriction; however, data on mutations in *IGF2*, encoding insulin-like growth factor (IGF) II, are lacking. We report an *IGF2* variant (c.191C→A, p.Ser64Ter) with evidence of pathogenicity in a multigenerational family with four members who have growth restriction. The phenotype affects only family members who have inherited the variant through paternal transmission, a finding that is consistent with the maternal imprinting status of *IGF2*. The severe growth restriction in affected family members suggests that IGF-II affects postnatal growth in addition to prenatal growth. Furthermore, the dysmorphic features of affected family members are consistent with a role of deficient IGF-II levels in the cause of the Silver–Russell syndrome. (Funded by Bundesministerium für Bildung und Forschung and the European Union.)

IGF-II IS A PEPTIDE HORMONE AND A MEMBER OF THE IGF FAMILY. IGF-I AND IGF-II regulate somatic growth and cell proliferation by binding and activating the IGF-I receptor (IGF-IR). Although both are expressed during fetal development, IGF-II is thought to have a major effect on embryonic growth, with IGF-I becoming predominant after birth.^{1,2} Studies of mice have supported a major role for the IGF receptor pathway in growth: knockout of *Igf1*, *Igf2*, or *Igf1r* results in growth retardation, whereas overexpression of *Igf2* results in overgrowth.^{3,4}

In humans, mutations in *IGF1* and in *IGF1R* have been implicated in intrauterine and postnatal growth retardation (Table 1).^{5,8-12} In mice, disruption of the paternal *Igf2* allele causes severe prenatal growth retardation, and an influence on postnatal growth has also been observed.^{13,14} Disruption of the maternal allele of *Igf2* has been found to have no effect on growth. This sex-specific influence is consistent with the fact that *Igf2/IGF2* is an imprinted gene. It is expressed from the paternal allele and not from the maternal allele in most tissues, including the placenta, although both the maternal allele and the paternal allele are expressed in the liver.^{15,16} Molecular alterations of the human chromosomal region 11p15.5, which harbors *IGF2*, are associated with the Silver–Russell syndrome (Online Mendelian Inheritance in Man [OMIM] number, 180860), a syndromic growth-retardation disorder. It has been hypothesized that deficient *IGF2* expression contributes substantially to the growth restriction in patients with the Silver–Russell syndrome.^{17,18}

Here, we report a paternally inherited *IGF2* nonsense mutation in four patients from one multigenerational family who had severe intrauterine and postnatal growth restriction and a Silver–Russell syndrome–like phenotype (Fig. 1 and Table 2; and the Supplementary Appendix, available with the full text of this article

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Table 1. Clinical Features in Patients with Growth Restriction Who Had Mutations in IGF1, IGF2, and IGFIR in Comparison with Patients with the Silver–Russell Syndrome Who Had ICR1 Hypomethylation.*

Characteristic	IGF1	IGFIR	IGF2	ICR1 Hypomethylation
Mode of inheritance	Autosomal recessive	Autosomal dominant	Genomic imprinting	Generally sporadic
No. of cases	3	>10	4 (1 family)	44
SDS for birth weight	-2.5 to -3.9	-1.5 to -3.5	-2.7 to -5.3	≤-2 in 82% of patients
SDS for birth length	-3.0 to -5.4	-0.3 to -5.0	-4.2 to -4.9	Not reported
SDS for weight at latest date	Not reported	-0.7 to -4.0	-2.2 to -4.7	Not reported
SDS for length at latest date	-4.5 to -9.0	-2.1 to -5.0	-1.6 to -4.0	≤-2 in 57% of patients
Microcephaly or macrocephaly	Microcephaly	Microcephaly	Relative macrocephaly	Relative macrocephaly (70% of patients)
Dysmorphisms†	None	Minor (3 patients)	Dysmorphisms associated with the Silver–Russell syndrome (2 patients)	
Triangular face	Not reported	Not reported	3 patients	59% of patients
Frontal bossing	Not reported	Not reported	3 patients	60% of patients
Micrognathia or retrognathia	Not reported	Not reported	3 patients	64% of patients
Low-set ears	Not reported	Not reported	2 patients	36% of patients
Clinodactyly V	Not reported	Not reported	2 patients	75% of patients
IGF-I level	Absent, deficient, or increased, depending on the nature of the mutation	High-normal to elevated	Normal	Not reported
IGF-II level	Not reported	Not reported	Deficient	Not reported
IGFBP-3 level	Normal or slightly elevated	In line with IGF-I levels	Normal or slightly elevated	Not reported
Growth hormone levels	Normal or elevated	Normal	Normal or elevated	Not reported
Response to growth hormone in the first year	No effect	Response (1 patient), partial response (2 patients), no effect (2 patients)	Response (Patients III.4 and III.7), partial response (Patient III.3)	Not reported

* IGF denotes insulin-like growth factor. IGFBP-3 [IGF-binding protein 3, and SDS standard deviation score. The cases associated with IGF1 mutation are reviewed by Netchine et al.,⁵ those associated with mutation in IGFIR are reviewed by Klammt et al.,⁶ and those associated with ICR1 hypomethylation are reviewed by Wakeling et al.⁷

† Only the major dysmorphisms in the Silver–Russell syndrome are listed.

at NEJM.org). The other family members, in particular the fathers of the patients and the paternal grandmother, were of normal height (Fig. 1).

PATIENTS AND FAMILY MEMBERS

PATIENT III.3

In the 43rd week of gestation, after an uneventful pregnancy, Patient III.3 (the index patient) (Fig. 1B), a boy with a body weight of 1730 g, was born spontaneously; he had hypotrophy and relative macrocephaly (size-at-birth reference data are provided by Niklasson and Albertsson-Wikland²⁰). The patient had a right ulnar ray defect (digits 3 to 5 were missing) and a contracture of the right elbow with a pterygium. He had severe feeding problems and needed to be fed through a nasogastric tube for the first 3 years of life. Psychomotor milestones were severely delayed (walking at 2.5 years of age, speaking single words at 3.5 years of age, and speaking sentences at 4.5 years of age). A neuropsychological examination performed with the use of the Kaufman Assessment Battery for Children at 12 years of age revealed low intelligence, with scores at or below the 5th percentile. A clinical examination at 4.5 years of age showed severe hypotonia and a high-pitched voice. His bone age lagged by 2 years. Growth hormone therapy was started when he was 9.6 years of age and was continued until he was 20 years of age. However, he had a relatively poor response, as judged from his height 1 year after the initiation of therapy. The onset of puberty in this patient occurred at 15.5 years of age.

PATIENT III.4

Patient III.4 (Fig. 1C) is the younger sister of Patient III.3. Fetal hypotrophy was first noted in the 30th week of gestation. A cesarean section was performed in the 36th week of gestation because of progressive oligohydramnion and fetal growth restriction; the patient's body weight at birth was 1345 g. Feeding through a nasogastric tube was necessary for 6 months. Her psychomotor development was slightly delayed. She was able to walk at 1.5 years of age and to speak single words at 2.3 years of age. A neuropsychological examination with the Kaufman Assessment Battery for Children at 7.3 years of age revealed low-normal intelligence, with scores at or below the 35th percentile.

At first presentation, when she was 4.2 years of age, the patient had severe growth restriction; she had a prominent forehead and clinodactyly of the fifth digit. Growth hormone therapy was started when she was 5.8 years of age and was efficacious in the promotion of growth. Her development during puberty was normal, with an age at menarche of 14 years. Growth hormone therapy was completed when she was 15.5 years of age.

PATIENT III.7

Patient III.7 (Fig. 1D) is the cousin of Patients III.3 and III.4. His parents are healthy. Poor fetal growth was first noted in the 30th week of gestation. A cesarean section was performed in the 36th week of gestation; the patient's body weight at birth was 1600 g. He had ambiguous genitalia with penoscrotal hypospadias and unilateral cryptorchidism. He reached milestones in development at the expected rate. He did not, however, have "catch-up" growth, and his bone age lagged by more than 2 years. Therapy with growth hormones was initiated when he was 6 years of age and was followed by growth. The onset of puberty occurred at 13 years of age. A neuropsychological examination with the use of the Kaufman Assessment Battery for Children at the age of 10 years revealed normal intelligence, with scores at or above the 50th percentile.

PATIENT IV.1

Patient IV.1 is the first child of Patient III.3. Her mother had short stature and intellectual disability due to an unbalanced X;8 translocation (partial monosomy X, partial trisomy 8). The mother's birth weight was 2160 g (standard deviation score at term, -3.5). She underwent growth hormone therapy and grew to an adult height of 147 cm (standard deviation score, -3.0).

Patient IV.1 was delivered by means of cesarean section at 35 weeks 4 days of gestation; her body weight was 1230 g. She had severe feeding problems during the neonatal period. However, insertion of a nasogastric tube for feeding was not performed, and her feeding problems mostly resolved during the first year. At the age of 18 months, she is able to eat at the table, chew solid food, and swallow without difficulty. She has relative macrocephaly with severe frontal bossing, small hands and feet, hypotonia, and

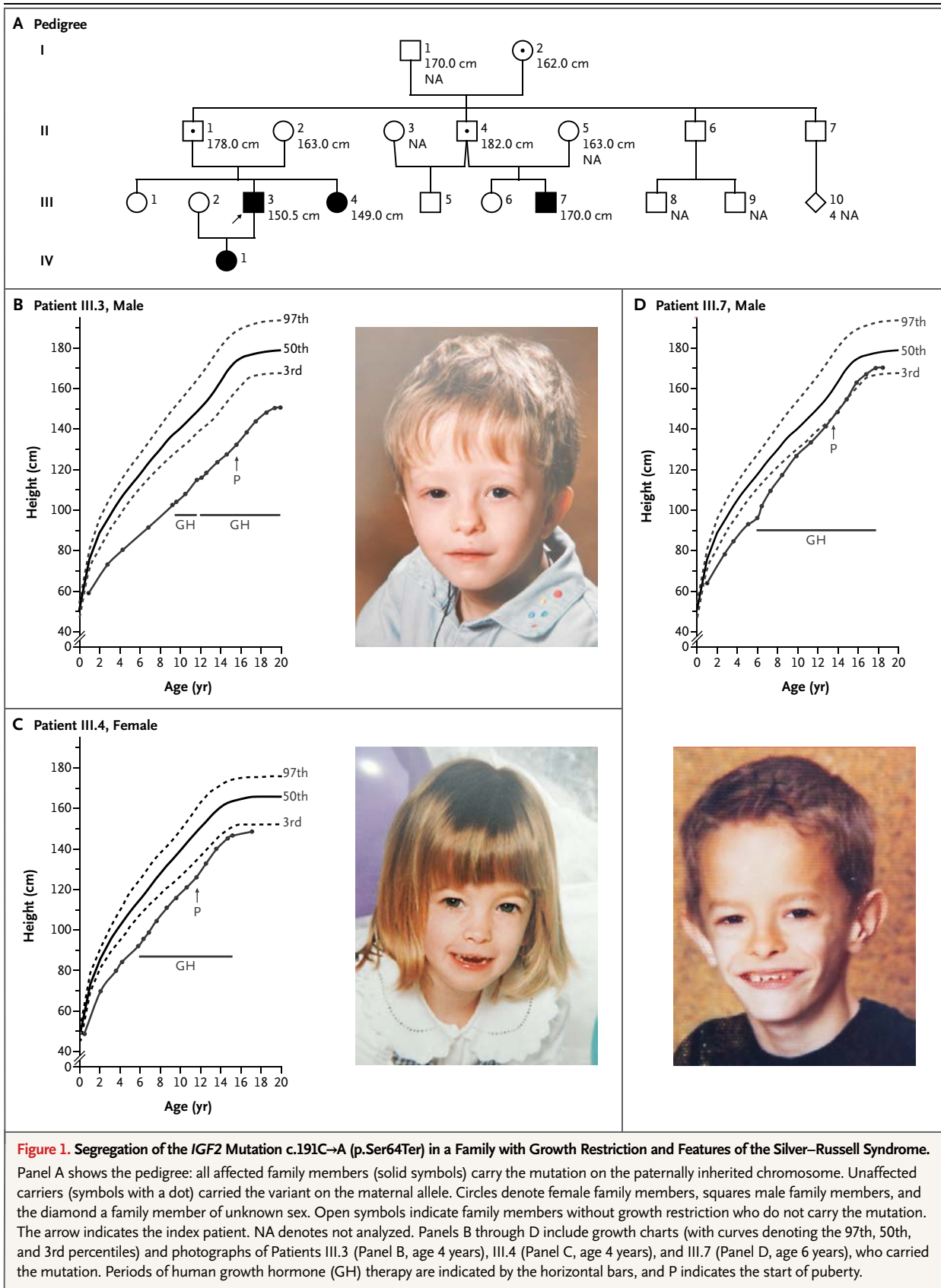


Table 2. Auxologic Characteristics and Endocrine Findings in the Four Affected IGF2 Mutation Carriers.*

Characteristic	Patient III.3	Patient III.4	Patient III.7	Patient IV.1
Sex	Male	Female	Male	Female
Body length at birth — cm (SDS)	43 (−4.9)	37.5 (−4.2)	40 (−4.8)	38 (−4.5)
Relative macrocephaly at birth†	Present	Present	Present	Present
Height at preschool age — cm (SDS)‡	82.1 (−6.0)	80.0 (−6.2)	93.0 (−4.2)	NA
Head circumference at preschool age — cm (SDS)‡	45.4 (−4.6)	47.0 (−2.5)	50.0 (−1.4)	NA
Adult height — cm (SDS)	150.5 (−4.0)	148.0 (−2.7)	170.0 (−1.6)	NA
Relative macrocephaly as an adult†	Present	Present	Absent	NA
Age at start and end of growth hormone therapy	9 yr 7 mo to 20 yr 1 mo§	5 yr 9 mo to 15 yr 5 mo	6 yr to 17 yr 9 mo	NA
Endocrine findings				
IGF-II level before growth hormone treatment — ng/ml¶	380	364	246	NA
At start of growth hormone treatment				
Height — cm (SDS)	104.0 (−5.6)	92.6 (−5.2)	96.3 (−4.2)	NA
BMI (SDS _{LMS})	11.6 (−4.4)	11.2 (−4.1)	12.1 (−3.9)	NA
Bone age — yr	5.0	3.5	2.5	NA
IGF-I level — ng/ml (SDS)	161 (−0.75)	174 (+0.92)	120 (+0.10)	NA
IGFBP-3 level — ng/ml (SDS)	2800 (−1.30)	4151 (+2.45)	2554 (+0.30)	NA
After 1 yr of growth hormone treatment				
Height — cm (SDS)	109.3 (−5.0)	100.9 (−4.1)	109.6 (−2.8)	NA
BMI (SDS)	12.0 (−3.8)	11.3 (−3.7)	12.0 (−3.3)	NA
IGF-I level — ng/ml (SDS)	397 (+1.46)	255 (+1.62)	235 (+1.38)	NA
IGFBP-3 level — ng/ml (SDS)	4707 (+0.56)	4001 (+2.08)	3541 (+1.68)	NA
At the time of presentation				
IGF-I level — ng/ml (SDS)	192 (+0.05)	NA	250 (+0.81)	NA
IGF-II level — ng/ml	448**	NA	504**	NA
IGFBP-3 level — ng/ml (SDS)	2522 (−1.55)	NA	2816 (−1.25)	NA

* NA denotes not assessed (Patient IV.1 was too young to be assessed). For additional data, see the Supplementary Appendix.

† Macrocephaly was defined as a value greater than +1.5 for the SDS of head circumference minus the SDS of body length.

‡ Measurements at preschool age were taken at the age of 4 years 6 months in Patient III.3, at the age of 4 years in Patient III.4, and at the age of 5 years 2 months in Patient III.7.

§ There was an interruption of 3 months during the second year of therapy.

¶ The level in Patient III.3, measured 14 months before the start of growth hormone treatment, was below the 5th percentile for his age (386 ng per milliliter); the 50th percentile for his age was 517 ng per milliliter. The level in Patient III.4, measured 3 months before the start of growth hormone treatment, was at the 5th percentile for her age; the 50th percentile for her age was 487 ng per milliliter. The level in Patient III.7, measured 24 months before the start of growth hormone treatment, was below the 5th percentile for his age (316 ng per milliliter); the 50th percentile for his age was 428 ng per milliliter.

|| The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. SDS_{LMS} was calculated with the use of the LMS method; see Cole and Green¹⁹ for additional details.

** The level was at the 10th percentile.

developmental delay. She is able to crawl and sit, but she does not walk. Her voice is weak and high-pitched.

STUDY OVERSIGHT

The study was approved by the ethics review board at the University Hospital Aachen, Aachen, Germa-

ny. All participants (patients and unaffected family members) provided written informed consent.

IDENTIFICATION OF *IGF2* MUTATION

After we ruled out in the affected family members molecular alterations that are known to be associated with the Silver–Russell syndrome²¹ (maternal uniparental disomy 7, ICR1 hypomethylation, submicroscopic imbalances, and *CDKN1C* mutations), we performed exome capturing with samples from Patients III.3 and III.7 and family members II.1, II.4, and III.1 with the use of the Ion Ampliseq Exome Kit, version 2 (Life Technologies), on an Ion OneTouch 2 instrument. The exomes were sequenced on an Ion Proton instrument with the use of Ion P1 chips and were processed with the use of Torrent Suite software, version 4.02 (Life Technologies). Variant calling was performed with the Torrent Variant Caller plugin, version 4.0.76860.

We filtered out all variants that were not shared by the affected patients and family members who were assumed to be carriers, as well as variants present in public databases (dbSNP build 138, 1000 Genomes, and the Exome Variant Server) and intronic, intergenic, and silent variants. Three prioritized variants were confirmed by means of Sanger sequencing, and we ruled out two of them (*TEX9* [NM_198524.1]: c.1096_1097dup, p.[Met367Argfs*18]; and *DYRK4* [NM_003845.2]: c.104C→T, p.[Thr35Ile]) because they did not segregate with the phenotype and obligate carrier status.

Finally, we detected a heterozygous nonsense substitution in exon 3 of *IGF2* (NM_001127598.2: c.191C→A), which was predicted to result in a premature stop codon (p.Ser64Ter). Segregation analysis showed that the patients inherited the mutation from their healthy fathers and that it originated from the healthy paternal grandmother. The occurrence of clinical features only in persons who inherited the variant allele through paternal transmission is a finding consistent with maternal imprinting of *IGF2*.

ENDOCRINE ASSAY

After extraction by means of the acid–ethanol method, IGF-II levels in serum were determined in the presence of an excess of IGF-I with the use

of a radioimmunoassay²² and were compared with age-related reference values (percentiles)²²; they were found to be deficient in Patients III.3, III.4, and III.7 (Table 2, and the Supplementary Appendix). In contrast, all three children had levels of IGF-I and IGF-binding protein 3 (IGFBP-3) that were near or above the median values of the reference population. IGF-I and IGFBP-3 levels were determined with the use of a radioimmunoassay,²² and the data were transformed into age-related standard deviation scores on the basis of a reference population of German and Danish children of normal height. Levels of growth hormone in serum were measured with the use of a polyclonal in-house radioimmunoassay calibrated against the World Health Organization International Reference Preparation 98/574 (1 mg=3 IU). The lower detection limit of the growth hormone assay was 0.1 μg per liter. The spontaneous secretion of growth hormone at night and after stimulation with arginine was found to be normal to high-normal. During growth hormone therapy, the levels of IGF-II in serum increased slightly, to the low-normal reference range.

DISCUSSION

We report a nonsense mutation (p.Ser64Ter) in *IGF2* in a family with some members who had prenatal and postnatal growth restriction (Fig. 1 and Table 2, and the Supplementary Appendix). If translated, the mutant protein would be approximately 30% of the size of the wild-type protein (64 vs. 236 amino acids; NP_001121070.1) and would not contain the IGF-I, IGF-II, and insulin receptor binding sites, but it is most probably targeted for nonsense-mediated decay.

Circulating IGF-II is, for the most part, synthesized by the liver, where, unlike in other tissues, *IGF2* is biallelically expressed. Patients had low levels of IGF-II in serum (Table 2). The fact that they had some, rather than no, IGF-II in serum is probably a result of the hepatic expression from the maternal *IGF2* allele.^{15,16} In nonhepatic tissues, such as the placenta, *IGF2* is expressed from the paternal allele only and acts in both an autocrine and a paracrine manner. The p.Ser64Ter mutation probably diminishes the synthesis and secretion of IGF-II in nonhepatic tissues.

Our findings support a role of IGF-II as a

prenatal growth factor.¹ However, we have not been able to determine whether the p.Ser64Ter mutation affects fetal growth directly, whether it affects fetal growth indirectly through impairment of placenta function, or whether it has both direct and indirect effects.

Postnatal growth might be affected through fetal programming, a hypothesis that states that insults sustained during pregnancy have permanent effects on adult health.²³ Of course, it is also possible that reduced levels of IGF-II in the serum, as well as the lack of or reduced synthesis of IGF-II in other tissues, might contribute to the postnatal growth restriction and the other clinical features of the patients. Because the bioavailability of IGFs is mediated by the balanced binding of IGFBP-3, a reduction in IGF-II might indirectly affect the influence of IGF-I on postnatal growth. The clinical appearance of the patients we describe here further corroborates the suggestion that *IGF2* insufficiency contributes substantively to the clinical features of the Silver–Russell syndrome (Table 1).

In conclusion, the identification of an *IGF2* mutation in patients with growth restriction indicates that IGF-II not only is a mediator of in-

trauterine development but also contributes to postnatal growth and has pleiotropic effects. Further studies are needed to confirm the contribution of IGF-II to prenatal and postnatal growth, as well as to estimate the extent of its contribution. A role of *IGF2* mutations in both growth restriction and overgrowth phenotypes is conceivable, as has been shown for functionally opposing mutations in *CDKN1C* in 11p15.5.²⁴ It is plausible that the timely identification of specific genetic mutations associated with growth retardation would make a type of “personalized” therapy possible. For example, a subcutaneous injection of recombinant IGF-II would be a logical therapeutic approach in the treatment of persons with IGF-II deficiency, although such treatment may not fully substitute for the autocrine and paracrine functions of the growth factor. Our findings also suggest that treatment with recombinant human growth hormone could be considered.

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