IGF1R, IGFALS, and IGFBP3 gene copy number variations in a group of non-syndromic Egyptian short children

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Abstract

Background: Insulin-like growth factor-1 (IGF-1) is required for normal intrauterine and postnatal growth, and this action is mediated through IGF1 receptor (IGF1R). IGF1R copy number variants (CNVs) can cause pre- and postnatal growth restriction, affecting an individual’s height. In this study, we used multiplex ligation-dependent probe amplification (MLPA) to detect CNVs in IGF1R, IGFALS, and IGFBP3 genes in the diagnostic workup of short stature for 40 Egyptian children with short stature.

Results: We detected a heterozygous deletion of IGF1R (exons 4 through 21) in 1 out of the 40 studied children (2.5%). Meanwhile, we did not detect any CNVs in either IGFALS or IGFBP3.

Conclusion: The diagnostic workup of short stature using MLPA for CNVs of IGF1R and other recognized height-related genes, such as SHOX and GH, in non-syndromic short stature children can be a fast and inexpensive diagnostic tool to recognize a subcategory of patients in which growth hormone treatment can be considered.

Keywords: Short stature, Copy number variations (CNVs), Multiplex ligation-dependent probe amplification (MLPA), IGF1R, ALS, IGFBP3

Background

Short stature is a condition in which the height of an individual is more than 2 standard deviation (SD) below the corresponding mean height for a given age and sex in a population [1]. Small for gestational age (SGA) is defined as a birth weight and/or birth length that is below −2.0 SD scores (SDS) for the gestational age in a certain population [2]. In the majority of short children, no final diagnosis can be reached, and they are categorized under idiopathic short stature (ISS) or SGA with failure of catch-up growth [3].

Insulin-like growth factor-1 (IGF-I) is essential for normal intrauterine and postnatal growth. The growth-promoting functions of IGF-I are mediated via the IGF1 cell receptor (IGF1R) [4, 5].

IGF1R is a tetrameric (α2/β2) transmembrane tyrosine kinase [6]. This receptor plays a pivotal role in the regulation of cell proliferation and metabolism and influences cancer development and life span [7–9].

The heterozygous mutations of the IGF1R gene lead to intrauterine and postnatal growth retardation and microcephaly. This mutation also causes a variable degree of psychomotor retardation and dysmorphic features [4, 10–12]. Meanwhile, individuals having homozygous deletion or mutation of IGF-1 suffer from profound intrauterine and postnatal growth failure, microcephaly, intellectual disabilities, sensorineural deafness, and dysmorphic features [3, 13, 14].

IGF1R copy number variants (CNVs) may lead to pre- and postnatal growth restriction. Several pure 15q26 monosomies, including those with breakpoints proximal to the IGF1R gene, have been described in the literature [11, 15–17].

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Circulating IGF-1 is bound to IGF-binding proteins (IGFBPs), mainly to IGFBP-3 and the acid-labile subunit (ALS), forming a ternary complex. ALS has a major role in stabilizing this ternary complex and extending the IGF-1 half-life markedly [18, 19]. Patients with ALS mutations have a markedly decreased IGF-1 and extremely low IGFBP-3 levels. These patients mostly show a moderately short stature, but the phenotype can be variable [20, 21].

Among the candidate genes for ISS are GH, GHR, STAT5B, and IGFALS; however, mutations in these genes are rare [22–25]. Meanwhile, the probable candidate genes for SGA include IGF1, IGF2, and IGF1R.

Growth hormone (GH) treatment can lead to a considerable height improvement in patients with IGF1R haploinsufficiency but not more than the expectation from the target mid-parental height [11, 26]. The multiplex ligation-dependent probe amplification (MLPA) was proposed as an economical screening assay to detect intragenic IGF1R deletions in short children given that appropriate genetic diagnosis will lead to the recognition of patients suitable for GH treatment [3, 12, 27].

In this study, we utilized MLPA as a rapid and inexpensive tool to detect CNVs in the IGF1R gene in the diagnostic workup of short stature. In this report, we describe a patient with a deletion of exons 4–21 in one allele of IGF1R gene and who presented to our clinic with short stature.

**Methods**

This study was conducted at The National Research Centre - Egypt over a period of 3 years and was approved by its Medical Ethical Committee. Informed written consent was obtained from parents of the included cases. A total of 40 short children were included in the study. Disproportionate short stature, such as Leri-Weill dyschondrosteosis/Langer mesomelic dysplasia syndromes and skeletal dysplasia, was excluded clinically. Chromosomal abnormalities, e.g., Turner syndrome, were excluded by conventional karyotyping. SHOX CNVs were excluded using MLPA assay [28].

Complete medical history was obtained with the general emphasis on the family history to construct a pedigree for three consecutive generations. Consanguinity status, family history of similar condition, and parental heights were documented. Physical examination and the nutritional status were carried out to exclude malnutrition status, systemic diseases, and clinically suspected syndromic cases. Birth weight, GH profile, bone age, and height in SDS were documented.

**MLPA assay**

DNA extraction from 3 ml peripheral blood lymphocytes from the 40 cases and reference samples (one reference for 7 patients sample with a minimum of three references per test) was carried out using the QIAamp® DNA Mini Kit, in accordance with the manufacturer’s instruction. The quality and quantity of the DNA samples were determined using a NanoDrop® spectrophotometer.

IGFIR, IGFALS, and IGFBP3 CNV evaluation was carried out using SALSA® MLPA® P217-B2 IGF1R probemix B2, following the manufacturer’s instruction (MRC-Holland) [29, 30]. This probemix contained 42 MLPA probes for IGF1R, IGFALS, and IGFBP3, with the amplification products between 127 and 472 nt. This probemix contained one probe per exon for exons 3 to 20, two probes for exons 1 and 2, and three probes for exon 21 for the IGF1R gene. The probemix also contained one probe for each exon of the IGFBP3 (five exons) and IGFALS (two exons) genes. In addition, a second probe for IGFBP3 exon 5 and for IGFALS exon 2 has been added. Eight reference probes were included in this probemix, detecting eight different autosomal chromosomal locations.

DNA denaturation and overnight hybridization of the MLPA probemix were performed, followed by probe ligation and amplification on the next day. The separation of amplified products was conducted using a Genetic Analyzer ABI 3500 (USA). The interpretation of the results was performed using the Coffalyser.Net® software (MRC-Holland). MLPA ratios less than 0.75 were considered as deletions, those between 0.75 and 1.30 as normal, and those with ratios more than 1.30 as duplications.

**Results**

The IGFIR, IGFALS, and IGFBP3 CNVs were studied in 40 short stature children. All our patients have normal karyotype and were screened for SHOX abnormalities and negative for SHOX CNVs. Our patients comprised 5 males and 35 females. Their age ranged between 2 and 16 years and their height between −2.0 and −6.5 SD. Exactly 19 out of the 40 patients (47.5%) had a positive family history of short stature (Table 1).

Heterozygous deletion of IGFIR exons 4 through 21 was detected (Fig. 1) in one patient (2.5%). He was born from a consanguineous marriage, diagnosed with intrauterine growth retardation (IUGR), and had a low birth weight of 1.7 kg (−3 SD). Upon examination at 4 years, his height was 86.5 cm (−3.8 SD) of his peers. He had microcephaly, head circumference of 46.0 cm (−2.9 SD), and a delayed bone age. The GH level and thyroid function tests and his IQ test yielded normal results. His karyotype was normal (Fig. 2). His mother (145.0 cm; −2.85 SD) and father were short (159.0 cm; −2.3 SD). His family history revealed a short cousin. However, no DNA was available to evaluate the detected CNVs in the family members.
| Patient No. | Sex | Age | Low birth weight | Consanguinity | Family hist. | SDS | GH |
|------------|-----|-----|------------------|---------------|--------------|-----|----|
| 1          | F   | 7   | +                | –             | +            | –2.75 | N  |
| 2          | F   | 8   | –                | –             | –            | –3.4 | N  |
| 3          | F   | 6   | –                | –             | –            | –2   | N  |
| 4          | F   | 6.5 | –                | +             | –            | –3   | N  |
| 5          | F   | 13  | –                | –             | –            | –3.1 | N  |
| 6          | F   | 11  | –                | +             | –            | –3.5 | N  |
| 7          | F   | 16  | +                | –             | +            | –2.8 | N  |
| 8          | F   | 10  | –                | +             | –            | –3.6 | Mild low |
| 9          | F   | 13.5| –                | +             | –            | –6.5 | N  |
| 10         | M   | 6   | +                | +             | –            | –5.6 | N  |
| 11         | F   | 15.5| –                | –             | –            | –3   | N  |
| 12         | F   | 12  | –                | –             | –            | –2.5 | N  |
| 13         | F   | 7.75| –                | –             | –            | –3   | N  |
| 14         | M   | 3   | –                | +             | –            | –5   | N  |
| 15         | F   | 2   | –                | –             | –            | –2.9 | N  |
| 16         | F   | 11  | –                | –             | –            | –3   | N  |
| 17         | M   | 12  | –                | NA            | NA          | –3.5 | N  |
| 18         | F   | 16  | –                | –             | +            | –3.5 | Low |
| 19         | F   | 10  | –                | –             | –            | –2.8 | N  |
| 20         | F   | 16  | –                | –             | +            | –2.9 | Low |
| 21*        | M   | 4   | +                | +             | +            | –3.8 | N  |
| 22         | F   | 8   | –                | +             | +            | –4.6 | N  |
| 23         | F   | 9   | –                | –             | +            | –3.4 | N  |
| 24         | F   | 15.5| –                | +             | +            | –3.3 | N  |
| 25         | F   | 12  | –                | –             | –            | –3.8 | Low |
| 26         | F   | 15  | –                | –             | +            | –4.3 | N  |
| 27         | F   | 11  | –                | –             | +            | –4.6 | Mild low |
| 28         | F   | 9.5 | –                | +             | +            | –2.5 | N  |
| 29         | F   | 12.5| –                | +             | –            | –3.9 | N  |
| 30         | F   | 12.5| –                | –             | –            | –3.7 | Low |
| 31         | F   | 13.5| –                | –             | –            | –3.3 | N  |
| 32         | F   | 9   | –                | –             | +            | –3.9 | Low |
| 33         | F   | 8   | –                | +             | +            | –4.1 | Low |
| 34         | F   | 16  | –                | +             | +            | –3.5 | N  |
| 35         | F   | 4.25| –                | –             | +            | –2.15 | N  |
| 36         | M   | 7   | –                | +             | +            | –2.75 | N  |
| 37         | F   | 11  | –                | +             | +            | –2.5 | N  |
| 38         | F   | 9.5 | –                | –             | +            | –3.3 | Low |
| 39         | F   | 8.5 | –                | –             | +            | –2.79 | Low |
| 40         | F   | 6   | –                | –             | –            | –2.5 | N  |

N = Normal
**Proband**
Discussion

IGF-1/IGFIR signaling pathway plays an important role in pre- and postnatal growth. The proper genetic diagnosis may result in an appropriate therapy.

IGFIR signaling is reduced in IGF1R haploinsufficiency, although occasionally, the IGF-1 response may remain normal. Further assessment of the bi-allelic expression of the IGF1R gene to reach the normal level of activity is needed [11, 31–33].

IGF1R haploinsufficiency may be the result of allelic loss of IGF1R due to chromosomal 15q26 deletions [16] or specific allelic IGF1R mutations that abrogate mRNA [3, 11, 32].

In our work, we detected the heterozygous deletion of IGF1R (exons 4 through 21) in a familial short stature patient identified from the 40 studied patients (2.5%). This finding was consistent with other group findings who found 2 in 100 SGA patients with IGF1R gene mutations in one study and detected 2 in 128 SGA patients with IGF1R heterozygous deletion in another research [3, 15].

Our patient had IUGR and was born SGA. This condition was in line with the clinical criteria that were proposed for heterozygous IGF1R mutations or terminal chromosome 15q deletions, including a small body size and head circumference at birth, short stature, and microcephaly later in childhood [15]. Moreover, a study detected a 50% reduction in the IGF1R expression on the cell surface by (fluorescence-activated cell sorting) FACS, and this result may explain the SGA phenotype [11].

In our research, we did not detect any patients with IGFALS CNVs. A study reviewed the work conducted on ALS complete deficiency in 61 patients from 31 families from different published reports and discovered that the 28 different mutations of the human IGFALS gene, including 17 missense, 7 frameshift, 2 in-frame insertions, and 1 nonsense mutation, are all located in exon 2. One patient had a deletion of the entire exon 2 [34, 35]. This finding may indicate the rarity of the CNVs of this gene and explain why no CNVs were detected in our study.

Given that IGFBP3 is the major carrier of IGF1, we investigated IGFBP3 CNVs. By reviewing the genetic causes for short stature, no specific diseases were connected to IGFBP gene alterations in humans [36]. IGFBPs have additional biological functions that are potentially independent of their IGF-binding properties, and growing evidence links them to diseases other than short stature [37–40]. Another study aimed to detect variations in the IGF family in 60,706 people from the Exome Aggregation Consortium and revealed that the loss of expression alleles are extremely low in IGF family genes including IGFBPs [40, 41]. Moreover, we did not find any IGFBP3 CNVs in our study group.
Conclusion

In spite of the small sample size, which is considered as a limitation, we identified a familial short stature case having a heterozygous IGF1R partial deletion in a group of Egyptian short non-syndromic patients. In the diagnostic workup of short stature, MLPA can detect the underlying genetic CNVs. Thus, screening with MLPA for CNVs of IGF1R and other recognized genes, such as SHOX and GH, that are considered as important regulators of individual height in non-syndromic short stature children can consequently become a fast and inexpensive diagnostic tool to recognize a subcategory of patients in which GH treatment can be considered. We recommend to carry on MLPA analysis for IGF1R after
exclusion of chromosomal abnormalities and SHOX CNVs.

Abbreviations

ACLS: ALS complete deficiency; ALS: Acid-labile subunit; CNVs: Copy number variants; GH: Growth hormone; IGF1R: Insulin-like growth factor 1 receptor; IGFBPs: IGF-binding proteins; IGF-1: Insulin-like growth factor-1; ISS: Idiopathic short stature; IUGR: Intra uterine growth retardation; MLPA: Multiplex ligation-dependent probe amplification; SGA: Small for gestational age

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Authors’ contributions

IF participated in the lab work and wrote the article and made the final submission. MR participated in the clinical selection of cases and reviewed the article. OE proposed the idea of the research and participated in the lab work and in writing the article. HE and IM selected the patients and performed the clinical assessment. All authors approved the final version for publication.

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Availability of data and materials

Data and materials are available upon request.

Declarations

Ethics approval and consent to participate

Ethical approval for this research was granted by National Research Centre Medical Ethical Committee (approval no. 16-274), in accordance with the ethical standards of the Declaration of Helsinki. Informed consent was obtained from parents of the included cases for history taking, examination, collection of samples, performance of molecular analysis, and scientific publishing of the data.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare.

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