Lessons from a patient carrying both an 11p paternal duplication and 15q deletion, illustrating the roles of IGF-II and IGF1R in growth regulation

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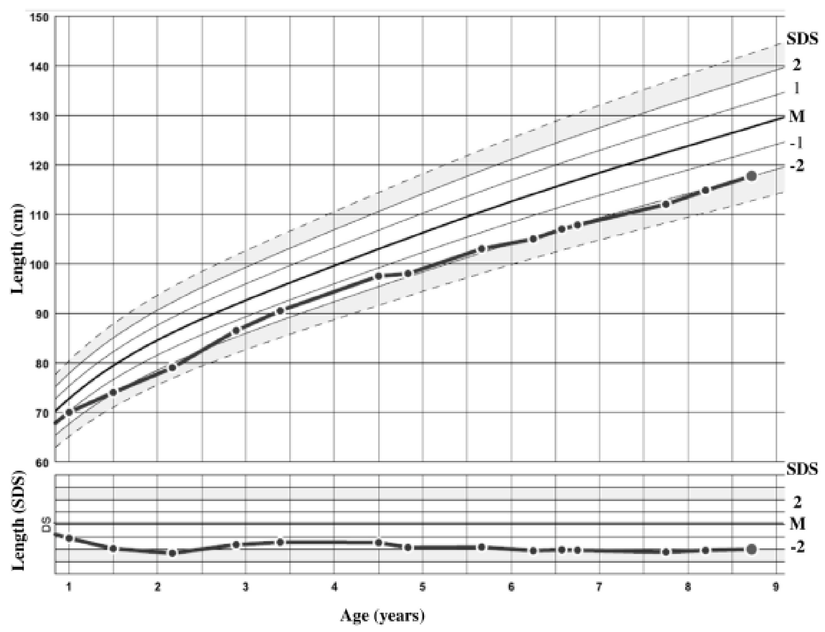
Introduction

The 11p15 region contains the *IGF2* gene, which is imprinted (expressed only from the paternal allele). Overexpression of *IGF2* leads to Beckwith Wiedemann syndrome (BWS), whereas loss of expression of *IGF2* leads to Silver Russell syndrome. IGF-II, as well as IGF-I, promotes growth through the activation of the IGF receptor type 1 (*IGF1R*), which is located at 15q26. *IGF1R* defects have been implicated for years as a cause of intrauterine growth retardation (IUGR) with microcephaly.
We report here a patient with postnatal growth retardation and a complex chromosomal rearrangement, including a distal 15q26.3-qter deletion, encompassing part of *IGF1R*, and a mosaic paternal duplication of the entire 11p15 region. Although the 11p duplication should have led to BWS, the patient presented with growth retardation, microcephaly, and intellectual disability, which is in accordance with the *IGF1R* disruption phenotype.

Clinical presentation

The patient was born after 36 weeks of amenorrhea with **normal birth weight** (2380 g, -0.6 SDS) and **microcephaly** (head circumference 30 cm, -2.4 SDS).
Target height was 159.5 cm (-0.7 SDS)
She presented with an early delay in language and cognitive development, strabismus, **short stature** and **microcephaly**



Biology

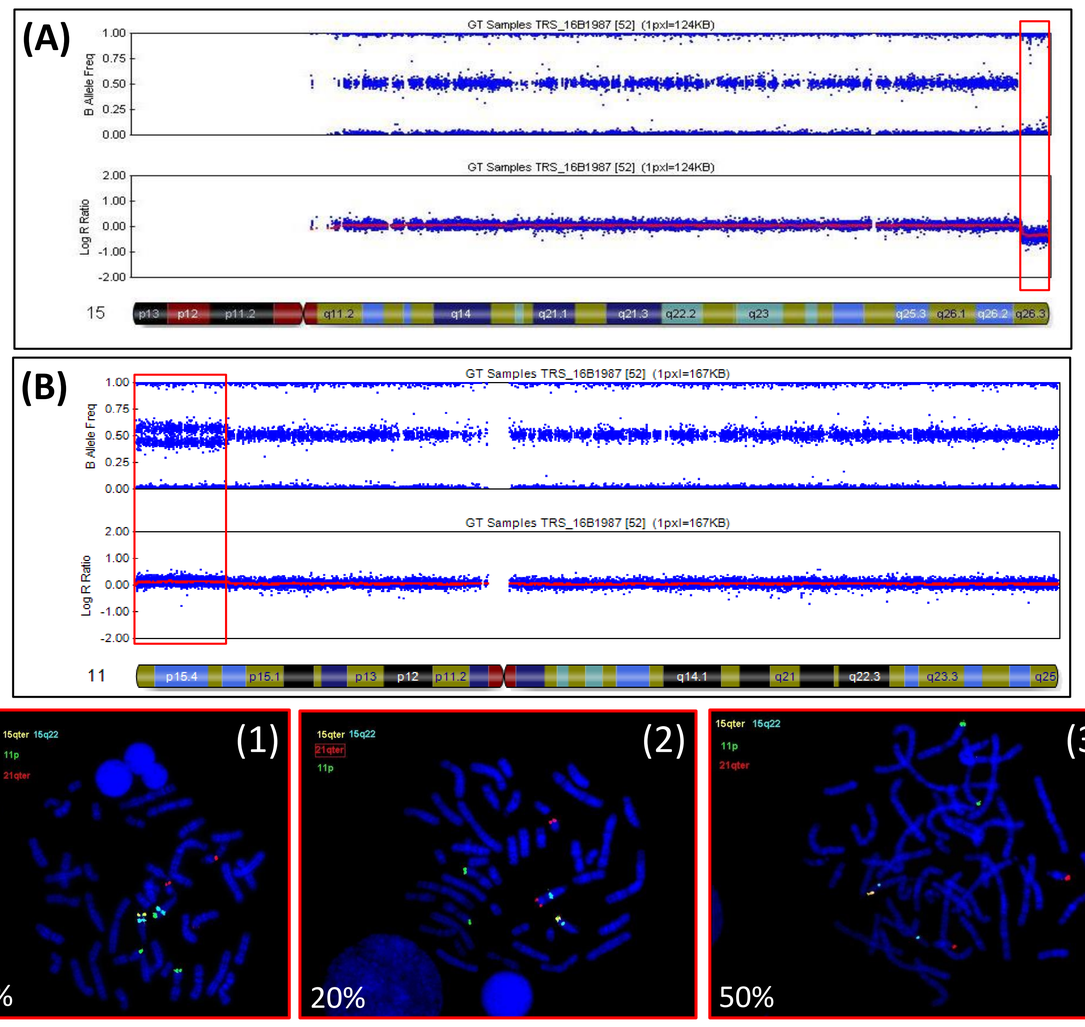
At 3 years, IGF-I level was in the upper range of the norm (145 ng/ml, +0.9 SDS) with elevated basal GH (45 mUI/L)
At 8 years, IGF-I level was high (345ng/ml, +2.1 SDS), with normal IGFBP-3 and a high level of ALS. This aspect is evocative of **IGF1 resistance.** Serum IGF-II was normal.

Genetic aspects

Karyotype: mosaic of
- 45,XX with a dicentric chromosome dic (15;21) and
- 46,XX cell line

SNP arrays:
- no copy number variation of chromosome 21
- a 15qter deletion, including a part of *IGF1R* **(A)**
- a 30% mosaic 11pter duplication, including *IGF2* **(B)**

FISH analyses: mosaic of
- unbalanced translocation t(11p;15q) resulting in **11p duplication** and **15q deletion (1)**
- 20%: unbalanced translocation t(15q;21q) resulting in **15q deletion (2)**
- 50%: **15q deletion (3)**



Discussion/Conclusion

IGF1R defects are usually associated with IUGR with microcephaly. We hypothesize that the overexpression of IGF2 (due to the duplication of 11p) compensates the IGF1R defect during fetal life, leading to normal birth parameters in this patient. In this case, IGF-II may signal through a pathway that is independent from IGF1R during fetal life.
After birth, the patient presented with short stature. This suggests that the IGF1R defect prevails over IGF-II overexpression, which favors a predominant role of IGF-II in fetal rather than in postnatal growth

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