

Maternal inheritance of an heterozygous exon 4

IGF I gene mutation (g.65941 G>A) in an IGUR child with mild post natal growth retardation

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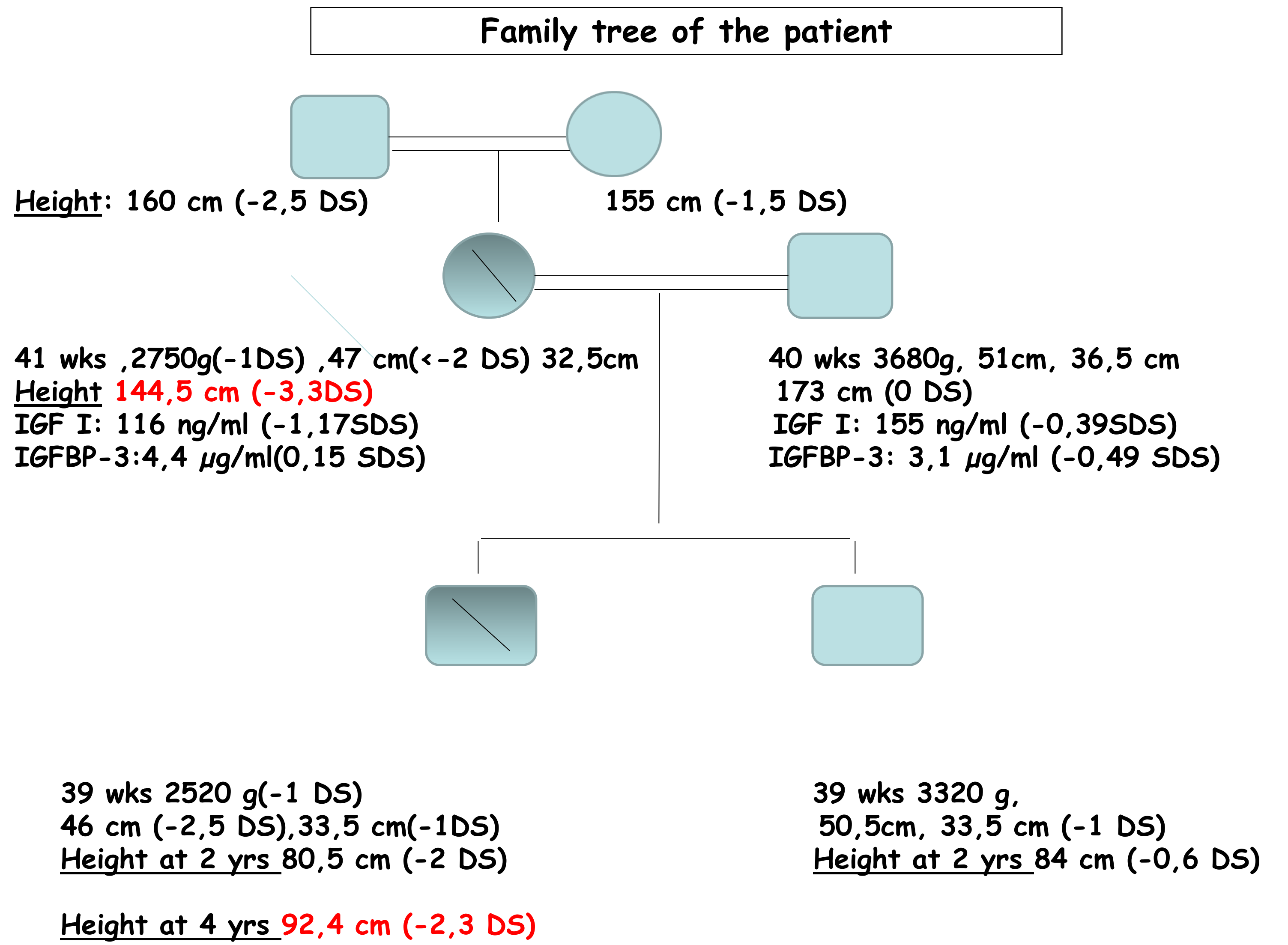
Disclosure status: nothing to disclose

Background: We already described a partial IGF1 primary deficiency due to an Exon 4 homozygous missense mutation (g.65941 G>A). A few patients are now characterized with an heterozygous IGF I deletion or mutation, questioning about IGF I haplo insufficiency role in short stature.

Objective and hypotheses: To depict the phenotype of a patient with a heterozygous IGF I gene to broaden the spectrum of IGF I primary deficiency.

Method: Parents informed consents were obtained in agreements to our local academic ethics committee for DNA analysis in their child.

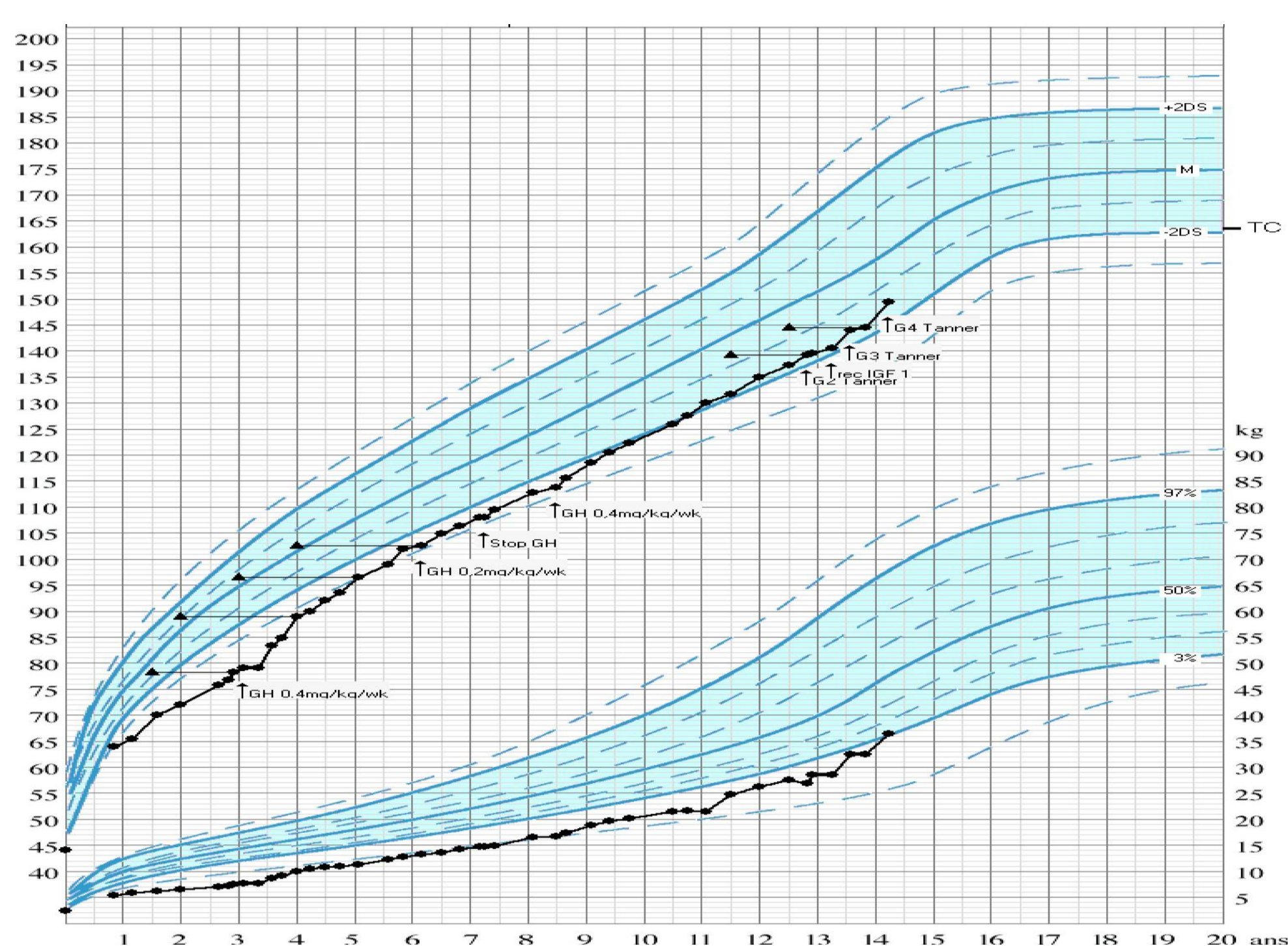
Results: We describe a boy born from consanguineous parents, with a intra uterine growth restriction (IUGR). Birth weight: 2520 g (-1 SD) Birth length: 46 cm (-2,5 DS) and Head circumference: 33.5 cm (-1 DS) at 39 weeks. Mother's height was 144,5 cm (-3.3 SDS) and father's height was 173 cm (0SDS). This child had an history of failure to thrive and gastro intestinal reflux. At presentation at 2 years, he had post natal growth failure, his height was at 80.5 cm, (-2 DS) and weight at 8.720 kg (-2 DS), and a normal head circumference (48 cm). He had no frontal bossing and no hemi hypotrophy. Penis and testes were normal. Dietician questionnaire showed poor proteins and calcium intakes. Usual nutritional markers and FreeT4, TSH levels were normal, IGF I was at 33 ng/ml (N 13-136)(-1SDS) in the lower range, contrasting with a mildly elevated IGFBP-3 at 3 µg /ml (N:0.95-3.35)+1.42 SDS. Direct sequencing of IGF I gene revealed an exon 4 heterozygous mutation g.65941 G>A that we had previously identified in some relatives of this new patient. We had demonstrated that the resulting protein (IGF1-R36Q) had a 4 times lower affinity to the IGF Receptor than the wild type. The heterozygous parents of our initial patient were shorter when the mutation was inherited from the maternal allele (-2.9 SDS) versus -1 SDS from the paternal allele. In this new patient, the molecular defect inherited probably from his mother, raises the question of its repercussion on the placenta function and on the foetal growth when present even at an heterozygous status only.



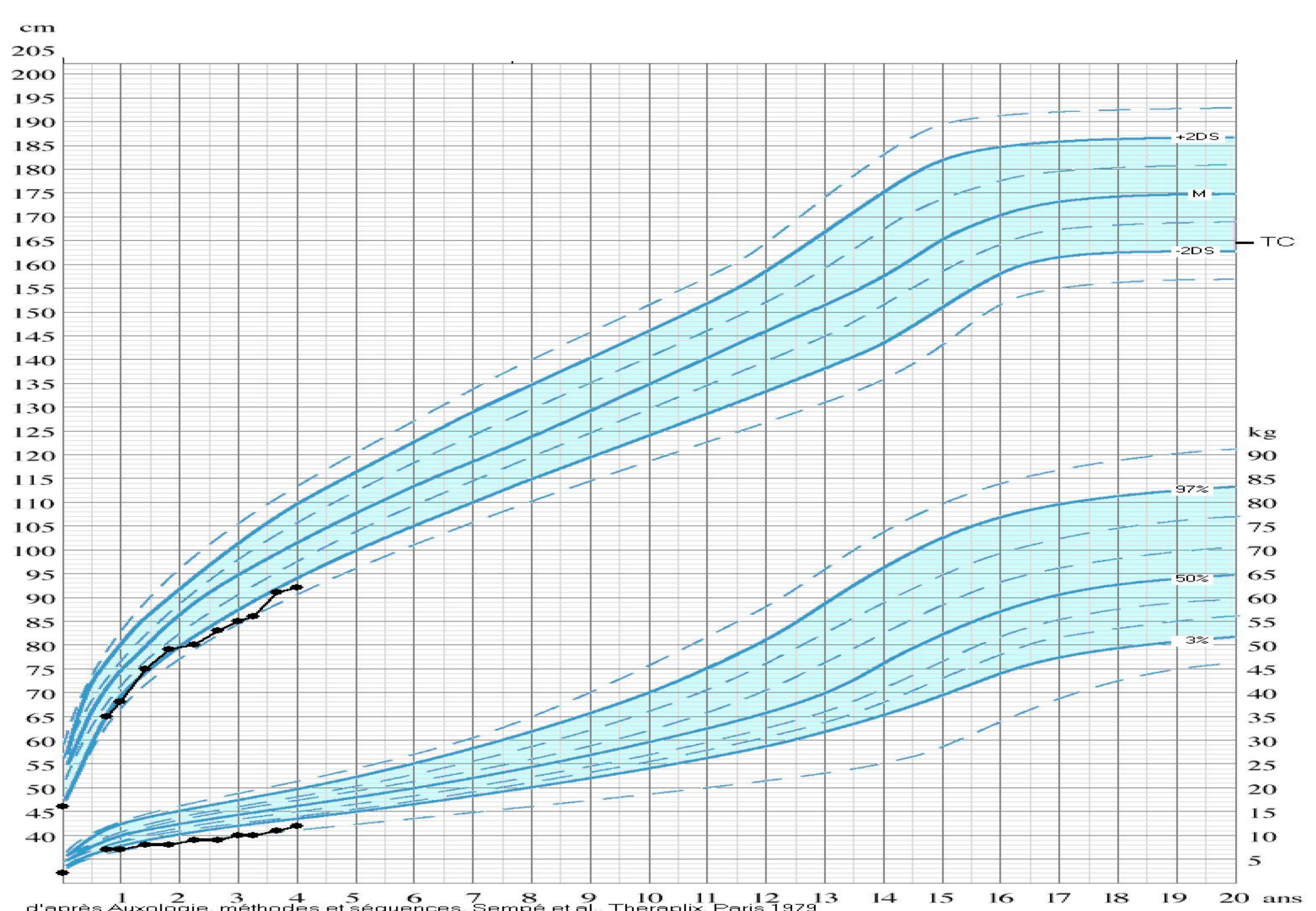
Picture of the patient



Growth chart of the homozygous relative



Growth chart of the heterozygous patient



Conclusion: Here is a new observation of a child born with IUGR and suffering from - 2,3SD post natal growth retardation and for whom we have identified an heterozygous IGF1 defect. We speculate that IGF I signaling may act in a dose -dependent way leading to a mild phenotype together with a maternal greatest impact in this case and/or a possible placenta dysfunction.