Nothing To Disclose

A Novel GHR Mutation, c.439+1 G>A ; in a Family with Laron Syndrome

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Background

- Mutations in the human GH receptor gene (GHR) are the most common cause of GH insensitivity (GHI) syndrome and IGF1 deficiency. The extracellular domain of GHR (encoded by exons 2–7 of the GHR gene) can be proteolytically cleaved to circulate as GH-binding protein.

Objective

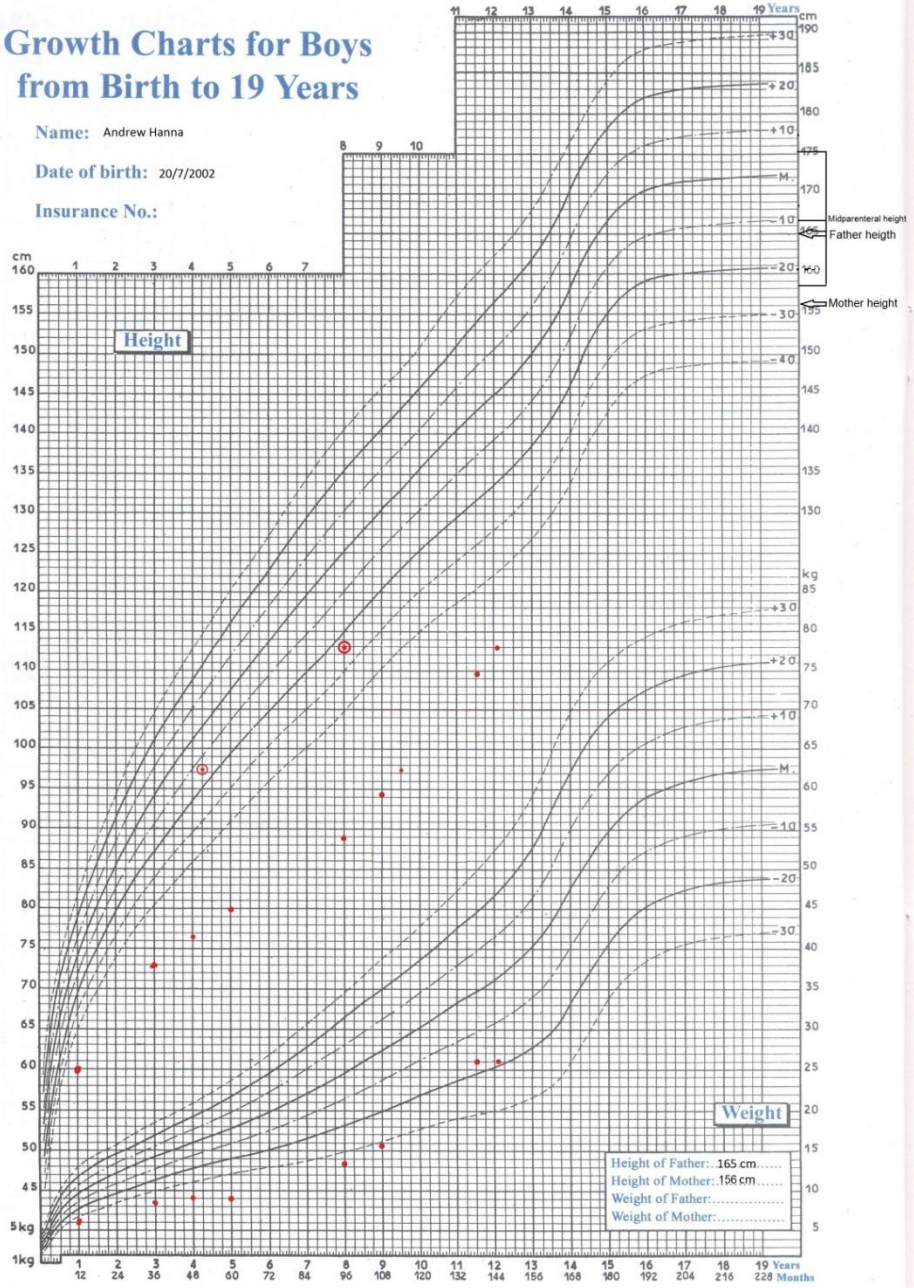
- To evaluate the cause of classical GHI (Laron) phenotypes in two siblings and their parents.

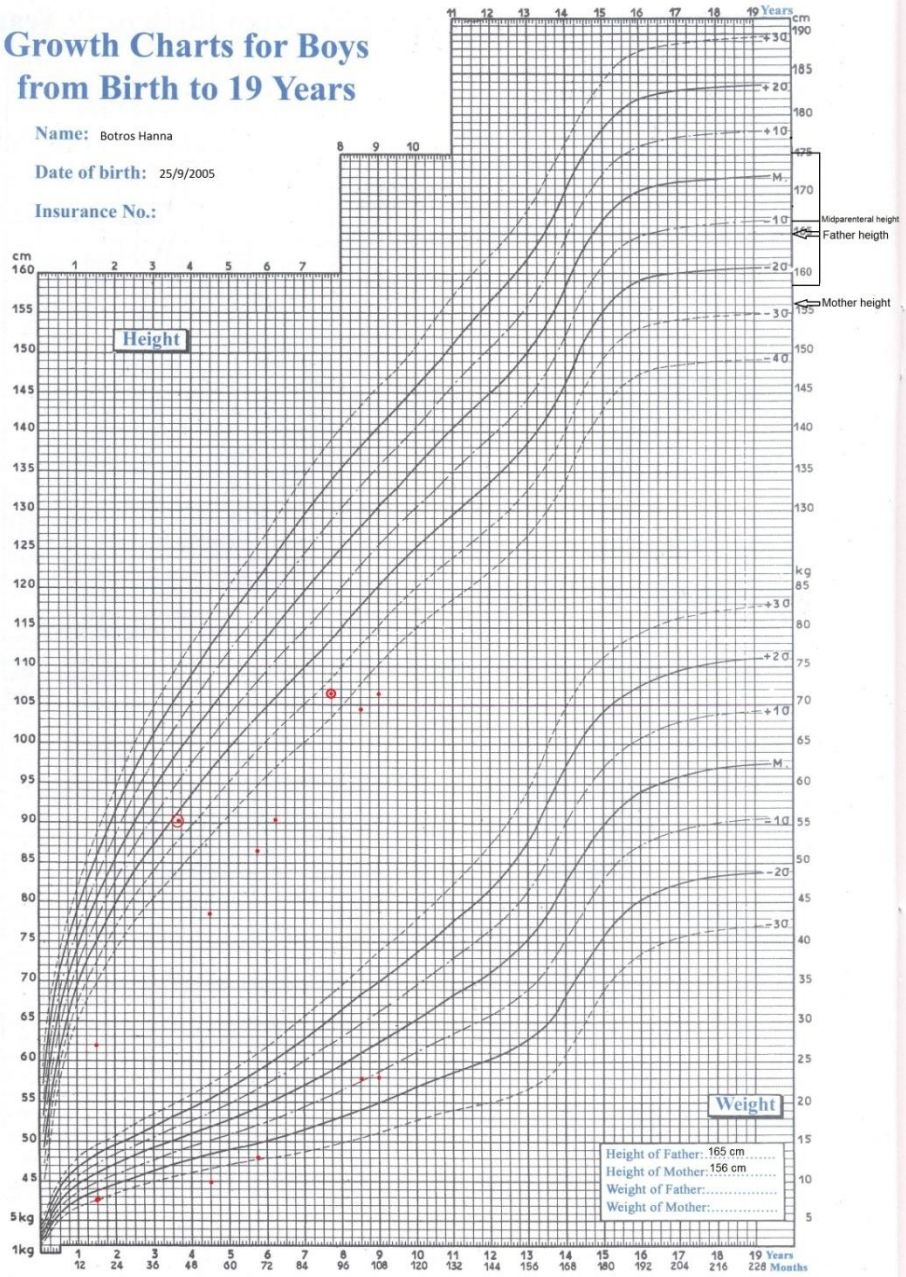
Method

- We observed clinical characteristics of two sibs with extreme short stature, assessed the function of GH–IGF1 axis, and surveyed their parents.
- Genomic DNA was extracted from peripheral blood, GHR mutation gene was amplified by PCR for sequencing, including exons and splicing areas.

Results

- Two full term brothers with average birth weight (aged 12.1 and 9 years) presented with extreme short stature.
- Height SDS was 6.00 and 4.00 S.D. respectively.
- The parents were consanguineous with normal stature (mother 156 cm, father 165 cm).
- Chronological age–bone age 4 and 1.3 years respectively.


Growth Charts for Boys
from Birth to 19 Years
Name: Andrew Hanna
Date of birth: 20/7/2002
Insurance No.:
Height
Weight
Midparenteral height
Father heigth
Mother height
Height of Father:..165 cm.....
Height of Mother:..156 cm.....
Weight of Father:.....
Weight of Mother:.....


Growth Charts for Boys
from Birth to 19 Years
Name: Botros Hanna
Date of birth: 25/9/2005
Insurance No.:
Height
Weight
Midparenteral height
Father heigth
Mother height
Height of Father: 165 cm
Height of Mother: 156 cm
Weight of Father:
Weight of Mother:
Years
Months

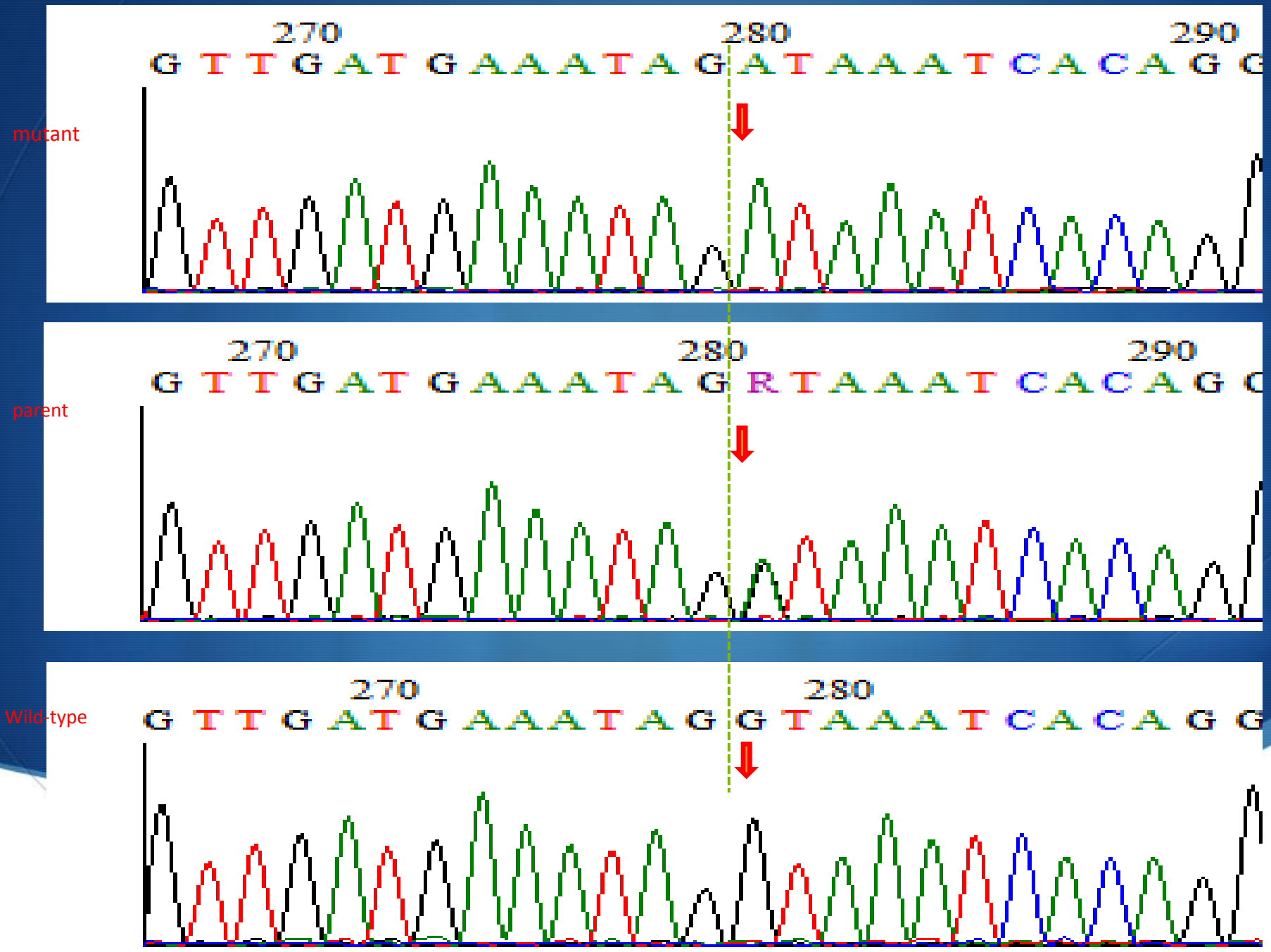
Results (Cont.)

- Peak GH for the two sibs; by glucagon was 33.3 and 15.7 ng/ml respectively.
- IGF1 for the older brother was: 9.5, 23.8, and 18.2 ng/ml;
- IGF1 for the younger was: 18.1, 28.6, and 22.2 ng/ml;

during IGF-1 generation test (reference range 98–156 ng/ml).

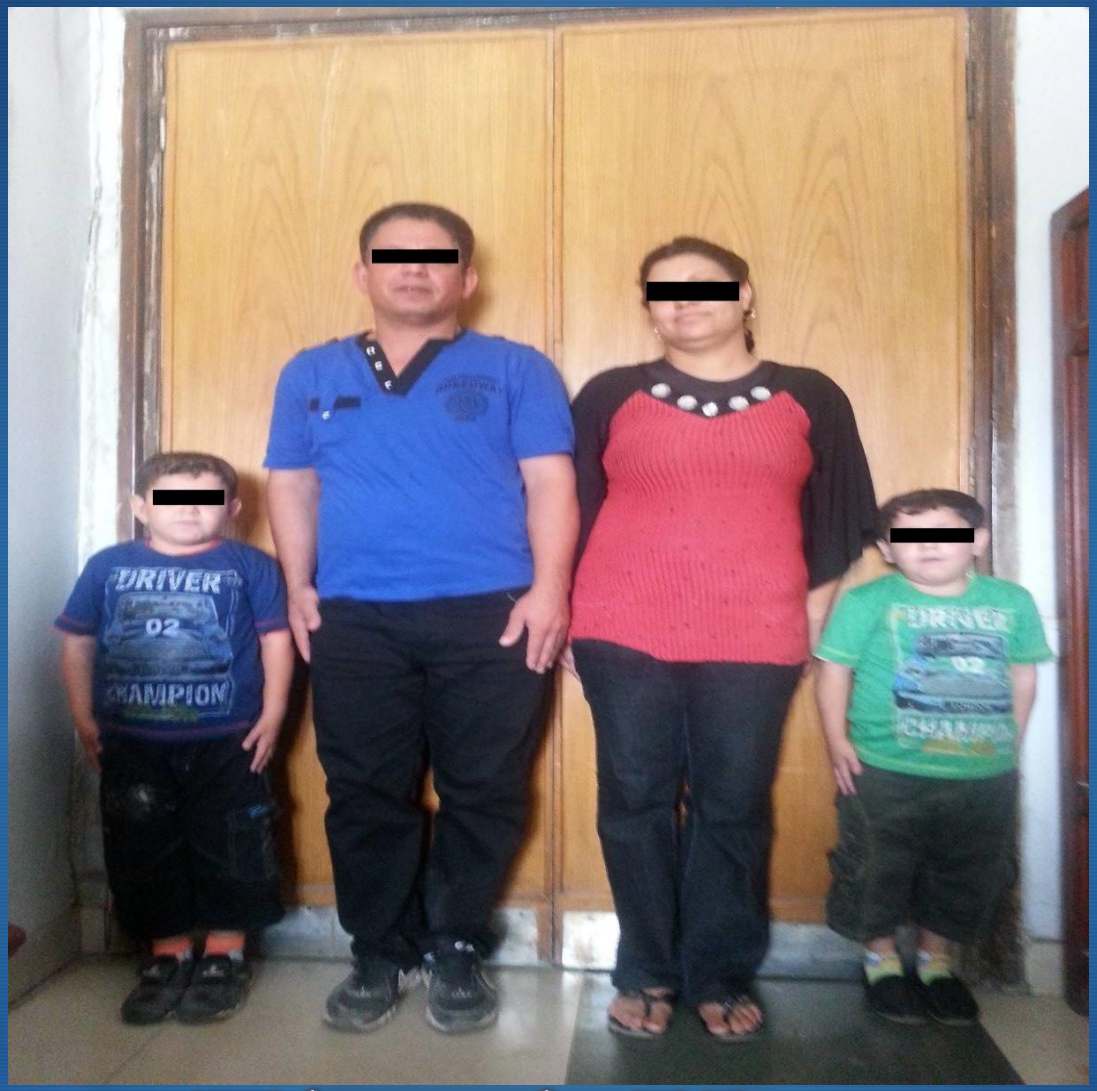
Mutation

- The two brothers were homozygous GHR mutation c.439+1 G>A, so a splice site mutation at the junction of exon 5/intron 5.
- It's novel and would be predicted to lead to skipping of exon 5, a frame shift and premature truncation of the protein also both parents were heterozygous for the same mutation.


mutant
270
280
290
G T T G A T G A A A T A G A T A A A T C A C A G G
parent
270
280
290
G T T G A T G A A A T A G R T A A A T C A C A G G
Wild-type
270
280
G T T G A T G A A A T A G G T A A A T C A C A G G

Conclusion

- The clarification of the molecular genetics for these defects will contribute to our future understanding of both normal and aberrant growth and avoid miss-diagnosis and maltreatment.



Thank You