# CHONDROCYTE REGULATING AND OTHER GROWTH PLATE GENES ARE INVALUABLE GROWTH REGULATORS: A STUDY ON CHILDREN WITH SHORT STATURE FROM 55 CONSANGUINEOUS FAMILIES

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## INTRODUCTION

Statural growth is regulated by multiple genetic, epigenetic and environmental mechanisms. The GH-IGF-1 axis was long believed to be the main linear growth regulator in children until more recent studies showed that the complex regulation of growth plate chondrocytes play an equal role. In order to extend our knowledge about the genes involved in short stature, we studied a unique cohort of children with short stature from consanguineous families living in Sulaymani in Kurdistan, Iraq.

## STUDY POPULATION

- Probands from 55 consanguineous families
- Height <-2.3 SDS at first examination (median -3.3 SDS; range -2.3 to -15 SDS)
- Median age 8 years (range 1 – 15 years)
- Examined at the endocrine outpatient clinic of the Department of Pediatrics, Sulaymani University College of Medicine between January 2018 and February 2020
- Four non-related patients were subsequently excluded due to the later diagnosis of Turner, Edwards and Silver-Russell syndromes.
- Therefore, 51 probands were included in the final cohort and 36 patients have been analyzed thus far.

## METHODS

- DNA was analyzed by Whole Exome Sequencing (WES) methods. The data were processed by a bioinformatic pipeline and detected variants were filtered using variant analysis software. Selected potentially pathogenic variants were confirmed using Sanger sequencing methods and evaluated by the American College of Medical Genetics (ACMG) standards.

## RESULTS

A monogenic cause of short stature was elucidated in 17 of 36 (47%) probands who were analyzed thus far.

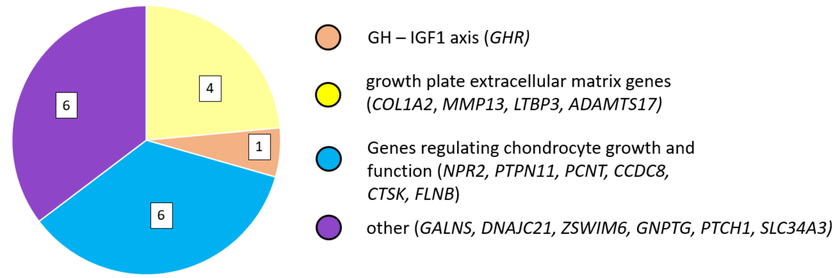


*Figure 1: Spectrum of genes causing short stature in our cohort*

| Patient ref. | Gene | Zygosity | Variant at cDNA level | Variant at protein level | Reference sequence | Published previously | ACMG |
|---|---|---|---|---|---|---|---|
| 11316 | *NPR2* | HET | c.2720C>T | p.T907M | NM_003995.3 | yes | P |
| 12559 | *COL1A2* | HET | c.1406G>C | p.G469A | NM_000089 | yes | LP |
| 11189 | *PTCH1* | HET | c.1664A>G | p.N555S | NM_000264 | no | LP |
| 11986 | *PTPN11* | HET | c.1403C>T | p.T468M | NM_002834 | yes | P |
| 11205 | *SLC34A3* | HOM | c.1058G>T | p.R353L | NM_080877.2 | yes | P |
| 12520 | *GNPTG* | HOM | c.494dupC | p.T165fs | NM_032520 | yes | P |
| 11293 | *CTSK* | HOM | c.894G>A | p.W298X | NM_000396.3 | no | P |
| 11263 | *GHR* | HOM | c.1807delT | p.S603fs | NM_000163 | no | P |
| 11215 | *DNAJC21* | HOM | c.983+1G>A | | NM_001012339 | no | P |
| 11824 | *LTBP3* | HOM | c.2223delC | p.A741fs | NM_001130144.2 | no | p |
| 11193 | *GALNS* | HOM | c.410T>C | p.I137T | NM_000512 | no | P |
| 11996 | *ZSWIM6* | HOM | c.3119G>A | p.R1040H | NM_020928.2 | no | LP |
| 11242 | *MMP13* | HOM | c.696C>G | p.H232Q | NM_002427.3 | no | P |
| 11285 | *ADAMTS17* | HOM | c.2086G>A | p.G696S | NM_139057.2 | no | LP |
| 12507 | *PCNT* | HOM | c.5767C>T | p.R1923X | NM_006031.6 | yes | P |
| 12590 | *CCDC8* | HOM | c.963delA | p.A323fs*156 | NM_032040.4 | no | P |
| 11223 | *FLNB* | HOM | c.7360G>A | p.V2454I | NM_001457 | no | LP |

*Table 1: Pathogenic or likely pathogenic variants in our cohort*

## CONCLUSION

Using WES methods, we successfully elucidated the genetic cause of short stature in 47% of probands analyzed thus far. More than half of the probands harbored a pathogenic variant in genes involved in regulation and function of chondrocytes, and / or encoding components of cartilaginous matrix. These results further strength the concept, that genes affecting the growth plate (chondrocytes and the extracellular matrix) play a crucial role in growth regulation.

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