# Whole Exome Sequencing Identifies a *GH1* Gene Mutation Causing Familial Isolated Growth Hormone Deficiency with Normal Peak Growth Hormone Concentrations

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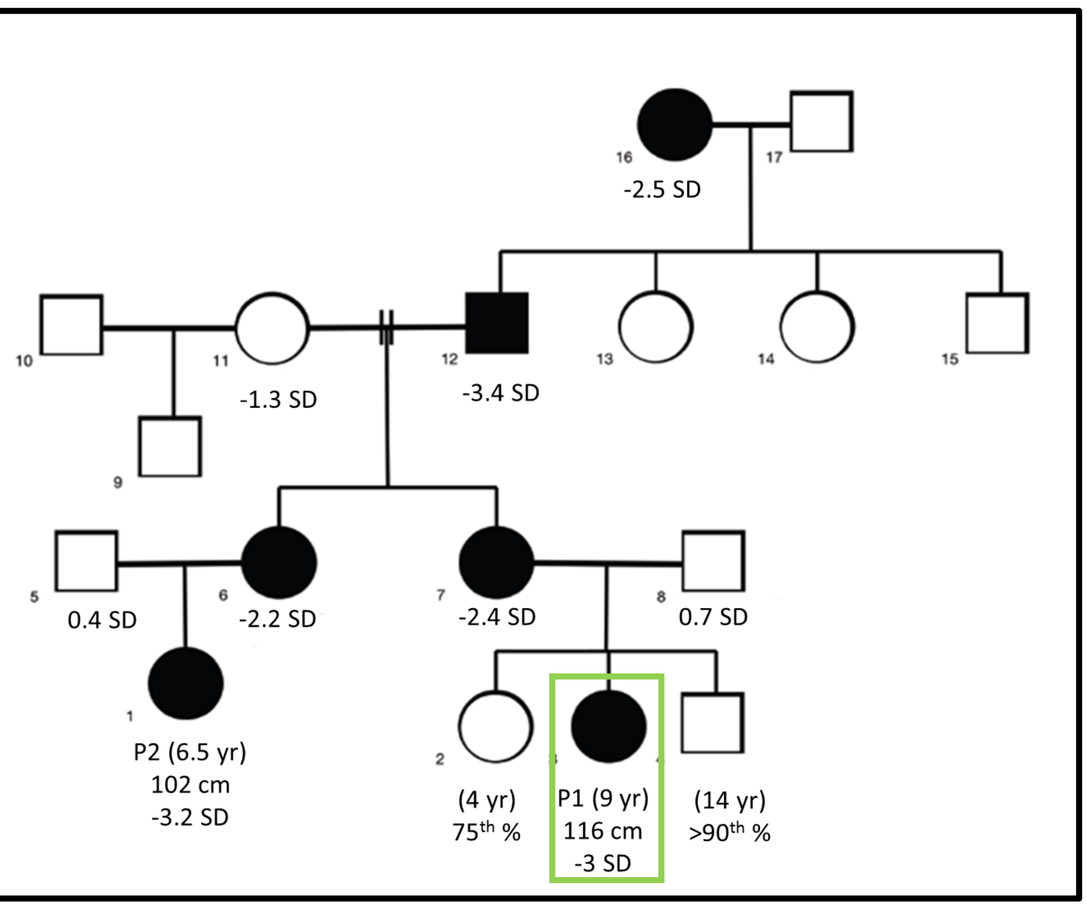
## INTRODUCTION

- Several pathologic conditions must be considered and ruled out in children with significant short stature.
- A large number of such children remain without a definitive diagnosis and are labeled as having idiopathic short stature (ISS).
- In a small proportion of the population, short stature is caused by specific genetic variations with large effect.
- Familial isolated growth hormone deficiency (IGHD) type II is autosomal dominantly inherited and caused by splice-site mutations and nucleotide substitutions in the *GH1* gene.

## OBJECTIVE

- This study aimed to identify the etiology of short stature in a four-generation family with dominantly inherited short stature.




## CASE PRESENTATION

- P1 presented at 9 years of age for evaluation of proportional short stature (-3 SD).
- Workup revealed low IGF-1 of 27 ng/ml (99 – 376) and IGFBP-3 of 1260 ng/ml (2769 – 4790).
- Growth hormone stimulation test was normal with a peak concentration of 15.9 ng/ml.
- Initially diagnosed with ISS.
- Strong family history of short stature appeared to follow an autosomal dominant mode of inheritance which prompted further investigation with WES.

The authors have no disclosures or conflicts of interest

## RESULTS

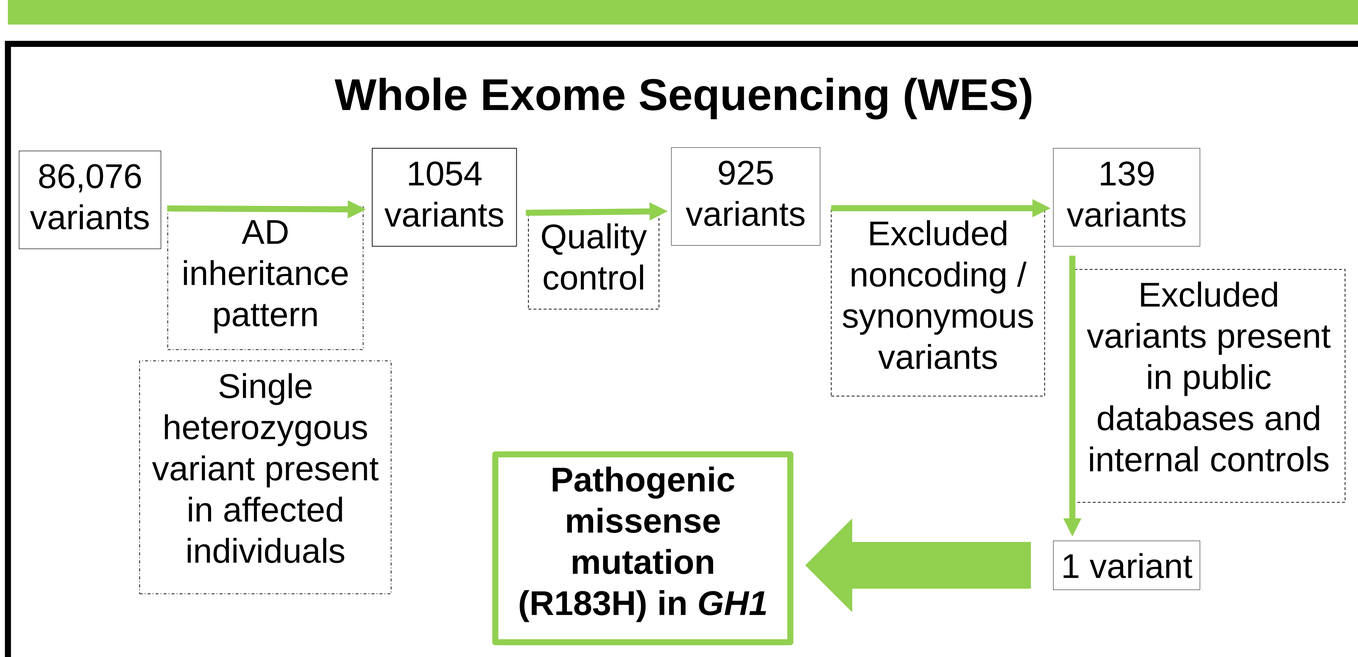



***Figure 1**. WES was performed in P1, P2, S1, B1 and GGMM. We identified the pathogenic variant R183H in GH1 which segregated in the affected individuals.*

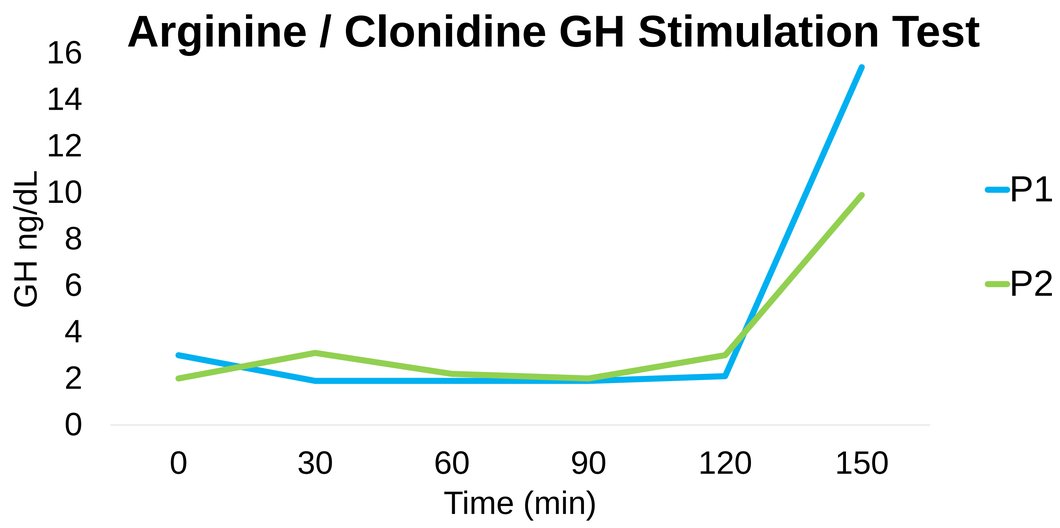



***Figure 2.** P1 and P2 underwent repeat GH stimulation tests and were found to have delayed peak GH responses. P1 had a peak GH of 15.4 ng/dL, and P2 had a peak GH of 9.9 ng/dL.*

## CONCLUSIONS

- WES rapidly identified a genetic etiology in this family with dominantly inherited short stature with normal stimulated growth hormone peaks.
- Genetic testing should be strongly considered in cases of familial short stature even when peak stimulated growth hormone concentrations are normal.
- The missense mutation R183H is a well described genetic variant that causes familial IGHD type II. Individuals with this mutation have releasable GH stores, but GH secretion is impaired resulting in short stature with a broad spectrum of phenotypes.
- It remains unclear whether or not adult patients with this mutation suffer the consequences of adult GH deficiency. We are implementing a protocol to investigate body composition, skeletal integrity, cardiovascular risk profile and the overall quality of life in the affected adults of this kindred.

## REFERENCES

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