Journal of Clinical and Medical Images

Clinical Image

ISSN: 2640-9615 | Volume 7

A Novel *GNAS1* Mutation with an Atypical Albright Hereditary Osteodystrophy Phenotype with Normal Weight and Cognition

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Received: 26 Feb 2024
Accepted: 06 Apr 2024
Published: 12 Apr 2024
J Short Name: JCMI

Citation:

Newfield RS, A Novel *GNAS1* Mutation with an Atypical Albright Hereditary Osteodystrophy Phenotype with Normal Weight and Cognition. J Clin Med Img. 2024; V7(13): 1-3

1. Introduction

A 10-year-old female presented for evaluation of short stature, with height <3% since age 3 years. On initial exam: height at 1%, BMI at 6%, with arm span 5.4cm <height. No goiter. Hands were small with short #4 and #5 metacarpals. Broad and short thumbs (Figure 1). Negative Madelung. Big toes were broad with syndactyly on the right, and webbing on the left between the #2 and #3 toes. The right foot has short #4 and #5, and the left has short #3, #4, #5 metatarsals (Figure 2).

Her presentation was suspicious for Albright hereditary osteodystrophy (AHO) [1,2] despite a normal BMI without cognitive deficits. Laboratory evaluation showed a 46XX karyotype, mildly raised TSH 7.18-11.43 uIU/mL (0.35-5.00), normal T4 and negative thyroid antibodies. She had elevated PTH=122.2 pg/mL (8.5-72.5) with calcium=9.5mg/dL (8.8-10.8) and normal phosphorus, without Vitamin-D deficiency. Normal IGF1 and growth hormone on provocative testing. Sequencing of the *GNAS*1 gene detected a heterozygote variant c.1180C>T (p.Leu394Phe) alteration in exon 13, in the last amino acid preceding the *GNAS*1 termination codon. This variant is not present in ClinVar, HGMD, or a locus specific database, or in the general population. PolyPhen2, a theoretical protein-prediction program ranks the change as «probably damaging». Another program (SIFT) predicts the protein change would be a "disease-causing mutation». While considered a variant of unknown significance, an updated genetics lab literature review (Dec 2022) stated that the last three amino acid residues of *GNAS*1 (Gsα) are essential for receptor-coupling [3] and may lead to protein instability. Patients previously termed pseudohypoparathyroidism (PHP) type 1C [3] are now named PHP1A [2].

2. Conclusion

we present case with a *GNAS*1 mutation that has PHP1A, and the commonly observed TSH resistance as well as short stature, and brachydactyly but without neurodevelopmental deficits or developing obesity (Figure 3) which are typical in AHO.

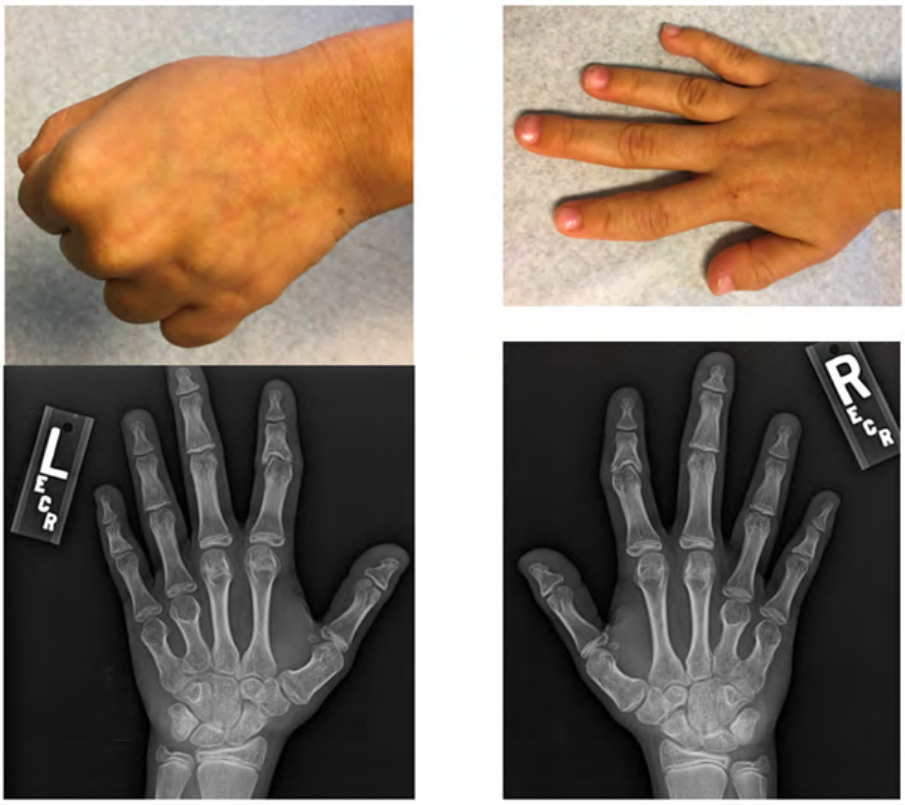

Figure 1: X-rays and pictures of both hands.

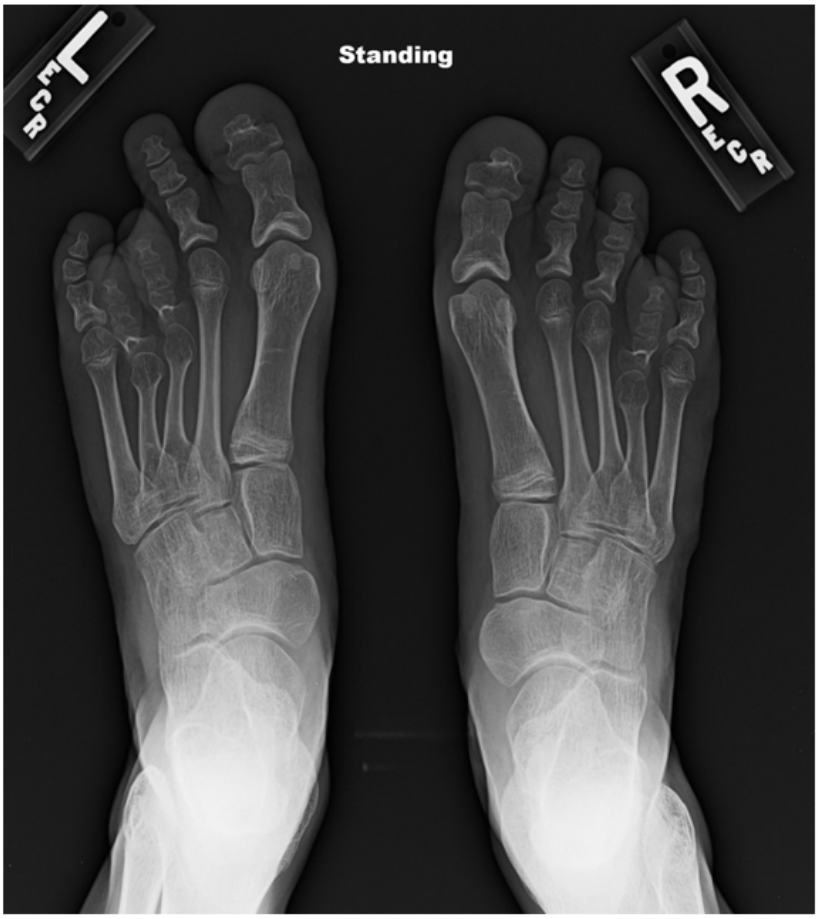

Figure 2: X-rays of both feet.

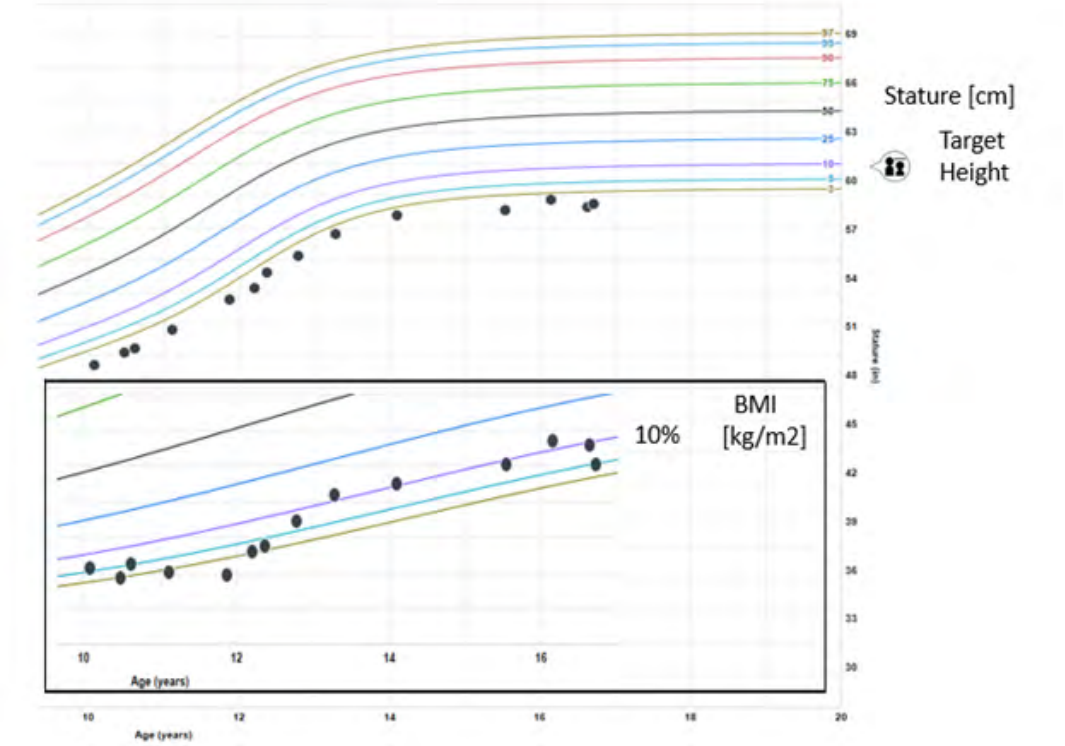

Figure 3: Height growth chart with body mass index (BKMI) as inset.

References

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