A novel GHR variant in the first patient of Indian origin with genetically proven growth hormone insensitivity

Sir,

Laron syndrome or growth hormone (GH) insensitivity is a rare disease presenting with severe postnatal growth failure.[1] Several cases of Laron dwarfism based on clinical and hormonal criteria have been described from India. However, no genetically proven cases of GH insensitivity have been reported from India to date. Clinically, GH insensitivity is usually indistinguishable from GH deficiency but can be easily distinguished by the usual hormonal investigations. However, differentiation of GH insensitivity from bio-inactive GH, the closest differential diagnosis of GH insensitivity, requires special investigations such as measurement of GH-binding protein (GHBP), insulin-like growth factor 1 (IGF1)-generation test,[2] or molecular testing for abnormalities in *GH1* or G*HR* genes.[3] Here, we report a case of GH insensitivity distinguished from bio-inactive GH using molecular testing which is also the first case of genetically proven GH insensitivity from India.

An 8-year-4-month-old boy, born to a non-consanguineous couple from lower socioeconomic strata, presented to the Endocrinology outpatient services, with poor height gain, noticed from the last 1.5 years. His birth weight was 3.0 kg with uneventful antenatal, perinatal, and postnatal periods. There were no similar complaints in the family. The developmental milestones were appropriate for age. There was no history suggestive of systemic disorders.

On examination, the height and weight of the child were 95.2 cm (-5.46 standard deviation score (SDS)) and 14 kg (-3 SDS), respectively. The upper to lower segment ratio was 1.02 (appropriate for age). The child had frontal bossing [Figure 1a], depressed nasal bridge, immature and cherubic facies, sparse and silky hair, small hands and feet, micropenis [Figure 1b] (stretched penile length: 2.5 cm), and testicular volume of 2 ml bilaterally. Bone age was 3.5 years [Figure 1c]. The first-line biochemical investigations (to rule out systemic disorders) and thyroid profile were normal. Serum IGF1 was undetectable (<15 ng/ml) whereas the baseline GH and peak GH levels after clonidine stimulation were 8.1 ng/ml and >40 ng/ml, respectively. The differential diagnoses of GH insensitivity and bio inactive GH were considered. IGF1-generation test could not be performed as the patient was from a remote place. Hence, a clinical-exome assay of deoxyribonucleic acid extracted from peripheral blood leukocytes was done using the Illumina sequencing platform which revealed a novel likely

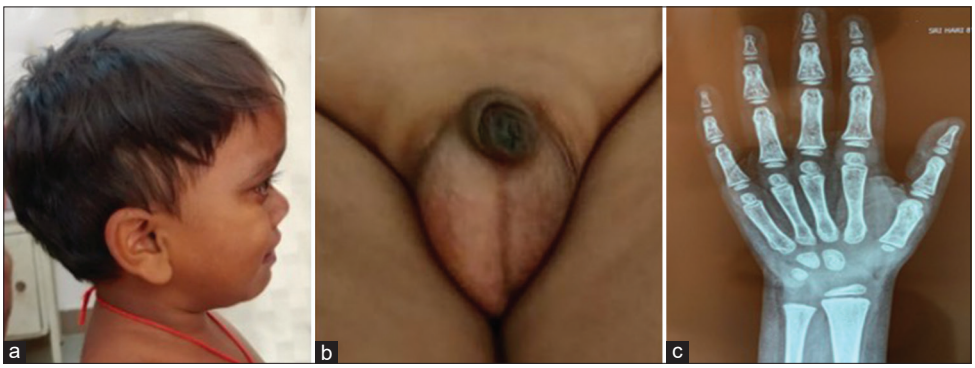

Figure 1: The immature facies with frontal bossing and midfacial hypoplasia (cephalo-facial disproportion) (a), micropenis (b), and retarded bone age (c) of the patient are depicted

pathogenic homozygous splice-site variant (c. 91 + 5G > A) in exon 2 of the *GHR* gene. The variant was predicted to be detrimental leading to loss of donor splice-site on in-silico analysis (Mutation Taster 2 and Natgene 2). The reference base is conserved across primates whereas the variant has not been reported in the 1000 genomes and gnomAD database. The variant was confirmed by Sanger sequencing and both the parents were heterozygous for the variant.

The case demonstrated the utility of molecular diagnosis to differentiate bio-inactive GH from GH insensitivity. However, the IGF1-generation test should be the preferred test over molecular diagnosis in this scenario as the former also predicts the clinical response of the patient to GH therapy. Recombinant IGF-1 (Mecasermin) is the treatment of choice in GH insensitivity; however it is not commercially available in India. Hence, the treatment could not be offered to this patient.

Here, we present the first patient of Asian Indian origin with a genetically proven GH insensitivity. Although, a few Indian children with 'GH insensitivity have been reported previously, none had a molecular diagnosis.[4,5] The literature on the genetic aspects of children of Indian origin with non-GH deficiency with short stature is limited. In a recent study from India, none of the 61 children with idiopathic short stature had a pathogenic/likely pathogenic variant in the *GHR* gene.[6] Further studies are warranted to explore the genetic etiology of short stature in children of Indian Origin.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 11-Jan-2022 **Revised:** 11-Feb-2022
Accepted: 16-Feb-2022 **Published:** 29-Apr-2022

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.ijem_24_22

How to cite this article: Nikith ZS, Sannappa RM, Sarathi V. A novel GHR variant in the first patient of Indian origin with genetically proven growth hormone insensitivity. Indian J Endocr Metab 2022;26:190-1.