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Case report

Severe Growth Hormone Deficiency in an Indian Boy Caused By a Novel 6 kb Homozygous Deletion Spanning the *GH1* Gene

Haris et al. GH1 Deletion Causing Familial Short Stature

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What is already known on this topic
- Mutations in *GH1* genes are associated with a rare condition called Isolated Growth Hormone Deficiency.
- The most common *GH1* deletions reported are 6.7 and 7.6 kb in size.
- The largest reported deletion is 45 kb in size.

What this study adds
- We report a 3 year old boy with extreme short stature with a deletion in *GH1* gene.
- The deletion is 6 kb in size which has not been reported before.
- The proband is homozygous for the deletion and the parents who are also short have a heterozygous deletion.

Abstract
Growth disorders resulting in extreme short stature are often a result of deficiency in growth hormone released from the pituitary gland or defective growth hormone releasing receptor. Genetic defects in the *GH1* and *GHRHR* genes account for around 11.1-20% of extreme short stature cases, resulting in a rare condition called Isolated Growth Hormone Deficiency. We describe the characterization of a *GH1* genetic defect discovered in a 3-year-old male patient with extreme short stature, developmental failure and undetectable serum levels of growth hormone. There is a familial history of short stature with both parents being short. Whole genome sequencing of the patient DNA revealed a large novel 6 kb homozygous deletion spanning the entire *GH1* gene in the patient. While the deletion was homozygous in the subjects, it was found in a heterozygous state in the parents. Thus we report a novel homozygous deletion including the *GH1* gene leading to Isolated Growth Hormone Deficiency- Type 1A associated with extreme short stature.
Keywords: *GH* gene deletion, Short stature, Familial short stature

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Introduction
Growth disorders resulting in extreme short stature are often a result of deficiency in growth hormone released from the pituitary gland (*GH1* gene, located on chromosome 17q23) or defective growth hormone releasing receptor (*GHRHR* gene, located on chromosome 7p14.3). Genetic defects in the *GH1* and *GHRHR* genes account for around 11.1-20% of extreme short stature cases, resulting in a rare condition called Isolated Growth Hormone Deficiency (IGHD). This frequency is reported to be 18.6 % higher in familial cases of IGHD [1].
IGHD is a disorder with varying prevalence in different populations ranging from 1:1800 in Sri-Lanka to 1:30,000 in the United Kingdom [2]. Familial IGHD is often grouped into 4 main subtypes: Type IA, Type IB, Type II and Type III [3]. These subtypes have a wide range in phenotype including extreme short stature, symptoms of doll-like facies, central obesity, highly pitched voices and puberty that is often delayed [4]. Type IA and IB often manifest as Extreme Short Stature (ESS) [3, 5] and follow an autosomal recessive or compound heterozygous inheritance pattern [6].
GH is a peptide hormone that contains two active sites for Growth Hormone Receptor (GHR) binding; a class I cytokine receptor. GHRs exist in a broad range of tissue cellular membranes including kidney cells, hepatocytes, adipocytes, myocytes, and many others. One GH molecule binds with two GHRs causing dimerization and this tertiary complex activates JAK-2 (Janus Kinase 2) bound to GHR [7]. Here JAK phosphorylates STAT5, a signal transducer and transcriptional activator, which enters the nucleus to induce GH-mediated genes expression. GH's mode of action relies on the secretion of IGF-1 from cells and stimulation of chondrocytes (cartilage cells) [8] leading to its differentiation. IGF-1 has an important role in stimulating growth at the end/growth plates of bones as well as muscle cells. In addition to the JAK-STAT pathway, the dimerization of GHR further causes the initiation of other cascades including the MAPK (Mitogen

Activating Protein- Kinase) pathway and the PI3K (Phosphoinositide 3 kinase) pathways. Thus, the deficiency of endogenous GH is directly linked perturbation of these pathways leading to short stature.
We report a 3-year-old male patient with extreme short stature and failure to thrive with a large novel 6 kb homozygous deletion spanning the entire *GH1* gene in the patient. We have also review all cases of *GH1* deletion previously reported and compared against our subject.

Clinical case presentation

We describe a 3-year-old male child of Indian origin who was born at full term via C-section with a birth weight of 2.8kg. The neonatal period was uneventful. At 6 months of age his parents noticed that he was not gaining weight. He was referred to Sidra Medicine at the age of 16 months for investigations of short stature. His weight was 6.80kg (0th percentile, -5.03 SDs, Figure 1) and his height was at 71cm (0th percentile, -5.4SDs, Figure 1). On examination he had severe frontal bossing, a pointed chin and a central incisor. There was no skeletal dysplasia, intellectual or developmental delay.
He underwent a growth hormone stimulation test (glucagon stimulation test) which revealed undetectable serum growth hormone levels. This suggests severe growth hormone deficiency most likely due to a defect in the *GH1* gene. His free T4 level was 11.8pmol/L [normal: 9.5-17.8pmol/L] indicated normal thyroid functioning. The pituitary MRI scan was structurally normal. The rest of the pituitary function tests were also normal. Table 1 shows the results of biochemical tests done.

Family history

His parents also have short stature, the father in particular (Figure 2) with a height of 152cm (-3SDs), while the mother's height was 151cm. The mid-parental height of the child is 158cm.

Follow-up and Management

The patient is following up with rhGH treatment at 0.029 mg/kg/day with a growth velocity of 10cm/year. His current height at age 3 years is 81.5cm and weight is 8.4kg.

Genetic testing methodology

Informed consent was obtained from patient and parents. DNA samples were extracted from peripheral blood specimen of subject and parents. Whole Genome Sequencing was performed on Illumina HiSeq platform using a 150-base paired-end single-index-read format. Reads in FASTQ files were then mapped to the NCBI human reference genome GRGh37/hg19 using Burrows–Wheeler Aligner (BWA-MEM) version 0.7.8. All subjects underwent variant calling using GATK(v3.6) and annotation was performed using SNPEff. Variants file was normalized and decomposed using vt. Additionally, vcfanno was used to annotate VCF file with extensive available data resources like gnomad, exomes.r2.0.2, gnomad.genomes.r2.0.2.sites, 1K genome, Exac etc. Genomic variants belonging to genes already known to be implicated in familial short stature were extracted.
Copy number variation of whole genome sequencing analysis detected a novel homozygous 6 kb deletion on the long arm of chromosome 17, 17q23.3 with coordinates (GRCh37/hg19 17:61993713-62000168) in our patient. The proband was homozygote for the deletion while the parents were heterozygotes for the deletion. This deletion was manually identified using integrated genome viewer (IGV) spans the entire growth hormone 1 gene (*GH1*), which is the main candidate gene and consistent with the phenotype of the patient (Figure 3a). We further confirmed the deletion using Samplot by visualizing and comparing the coverage of the structural variant with the surrounding regions (Figure 3b)

Discussion

Type IA is the second most reported type of IGHD; these cases often have a variety of mutations involving the *GH1* gene [3] specifically, 66.7% of familial cases of IGHD Type 1A involve *GH1* aberrations [6]. Eighty percent of reported *GH1* deletions are of the 6.7 kbs size, while many others are of 7.6 kbs in length [9,10]. These deletions are caused by imbalanced recombination between 98% homologous 454-592bp flanking regions of the *GH1* gene [9, 11]. Due of these mutations, IGHD Type 1A patients will often have undetectable serum levels of GH due to a lack of endogenous GH and rhGH treatment will often lead to antibody response against GH [3, 10, 12]. Affected proportionate short stature patients will have heights ranging from -3SDs to -9.6SDs [6]. This was observed in our patient as well with undetectable serum growth hormone levels on stimulation testing.
Our genetic testing also revealed that both parents are affected with short stature even though they only have 1 identical copy of the deletion, indicating that possibly heterozygous deletions in *GH1* may also contribute to the defects in short stature, however we could not find any previous reports of heterozygous deletions of *GH1* causing short stature.
We performed an electronic literature review of the PubMed database to identify relevant articles about *GH1* that lead to short stature written in English, published up to March 2022. The following terms were used to search the database: "growth hormone 1 gene deletion", "*GH1* deletion", "pituitary growth hormone gene deletion", "IGHD1A and deletion", and "short stature". We identified 20 articles with *GH1* deletion. Table 2 shows full list of deletions with clinical phenotype and size of deletions. These studies included different ancestries (Europeans, Asians, South/North Americans, and Arabs), however, most of the studies were conducted in European populations. Majority of the patients were diagnosed with severe short stature in early infancy. Our analysis showed that the most common size of *GH1* deletion reported is 6.7 and 7.6 kb and the largest deletion reported is 45 kb in size. Majority of the subjects displayed a similar phenotype with development of GH antibodies after hGH therapy after varying durations of therapy. Most of the patients with 6.7 kb deletion frequently develop GH antibodies in response to GH therapy while patients who carry the 7.6 kb deletion tend to have lower immunological intolerance when treated with exogenous GH. Overall, there is heterogeneity in developing GH antibodies even within the same family members. Our subject is still young and has been on GH therapy for 2 years with promising increase on height but not weight gain. A limitation of our study is that GH antibodies could not be measured.

Conclusion

We report a 3-year-old male patient with extreme short stature and failure to thrive with a family history of short stature. Growth hormone levels were undetectable with Whole genome sequencing revealing a large novel 6 kb homozygous deletion spanning the entire *GH1* gene in the patient leading to Isolated Growth Hormone Deficiency- Type 1A associated with extreme short stature.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

B.H. collected patient information, recruited the patients, analysed and interpreted the data and drafted the manuscript. K.H. designed the study, obtained funding, reviewed and edited the manuscript. I.M. and U.U. analysed genetic data and drafted the manuscript. D.S. recruited the patient and reviewed the manuscript.

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Table 1 results of biochemical tests done on the patient at the time of recruitment

Test	**Patient results**	**Reference level**
Growth hormone at 0, 60, 120, 180 mins (mcg/L)	Undetectable	>10mcg/L at any time point
IGF-1 (ug/dL)	Undetectable	0.06-0.57
IGF binding protein-3 (mcg/mL)	<0.5	0.7-3.6
Morning ACTH (pg/mL)	146	7.2-63.3
Random Blood Glucose (mg/dL)	82.8	70-110
Total Calcium (mg/dL)	10.2	8.8-10.8
TSH (mIU/L)	3.61	0.76-4.64
Free T4 (ng/dL)	0.92	0.74-1.38
Prolactin (mIU/L)	302	70-390
Cortisol (ug/dL)	7.94	2.17-12.79

Table 2 Deletion size and phenotype of all reported subjects with GH deletion causing short stature

	Deletion Size	Deletion Zygosity	Phenotype
1	7.5 kb [10]	Homozygous	-Reported four patients from three families with severe IGHD. -Extreme short stature. -Absence of hGH production. -Formation of hGH-antibodies in high titers after hGH therapy.
2	7.5 kb [13]	Homozygous	-Reported four unrelated Jewish patients with IGHD. -All patients carry 7.5 kb deletion. -All four patients showed good response for human growth hormone (hGH) therapy
3	6.7 kb and 7.6 kb [14]	Compound heterozygous	-Severe growth hormone deficiency, truncal obesity, acromicria, low IGF-I and IGFBP-3 and severe anterior pituitary hypoplasia
4	6.7 kb and 2 bp [15]	Compound Heterozygous	-Severe growth deficiency -GH therapy resulted in catch-up growth at 9 years and 2 months with development of anti-GH antibodies
5	7.6 kb [16]	Homozygous	-Two sibling patients with short stature -Responded well to GH substitution. -No formation of blocking antibodies occurred. -GH1 and CSHL1 gene affected by the deletion.
6	6.7 kb and 7.6 kb [17]	Homozygous	-A patient with IGHD -Very low response of GH secretion. -Undetectable levels of IGF-I and IGFBP-3. -MRI showed a severe anterior pituitary hypoplasia.
7	6.7 kb or 7.6 kb [9]	Homozygous	-Ten patients with either 6.7 kb (8/10) or 7.6 kb (2/10) deletions -3 North European, 3 Mediterranean and 4 Turkish patients -All the patients presented with severe growth retardation, decreased growth rate, and retarded bone age
8	45 kb [18]	Homozygous	-An Italian family 3 affected IGHD patients. -These three patients showed heterogeneity in growth response and antibody formation in hGH replacement therapy.
9	45 kb [19]	Homozygous	-A Turkish family with three affected boys presenting with growth retardation. -The deletion involved Growth hormone and somatotropin gene clusters.
10	40 kb [20]	Homozygous	-A French family with two affected siblings, with severe congenital growth deficiency. -Both patients developed antibody after the hGH therapy
11	6.7 kb [21]	Homozygous	-A girl with short stature and cystic fibrosis. -Developed anti hGH antibodies after 2 months of hGH replacement
12	7.1 kb [22]	Homozygous	-A Chilean patient with short stature and repeated hypoglycemic episodes (neonatal period). -hGH treatment discontinued after the patient developed anti hGh antibodies and switched to IGF-1 treatment.
13	3.8 kb [23]	Homozygous	-A patient with severe congenital GH deficiency. -Non-Detectable Plasma GH levels in response to pharmacological stimulation tests. -A round face, small nose with depressed nasal bridge -Treated with biosynthetic methionyl (met) GH but developed antibody after 5 years.
14	6.7 kb [24]	Homozygous	-Three Indian siblings with short stature. -Patients carried exactly same deletion but showed heterogeneity in rhGH treatment response.
15	22 kb and c.10 + 1G>T [25]	Compound Heterozygous	-A 1 year and 9 months patient with growth retardation. -Auxiliary examinations showed low GH, low IGF-1 and elevated TSH
16	6.7 kb and/or 7.6 kb [26]	Homozygous And compound heterozygous	-12 patients with IGHD: -10/12 (homozygous 6.7 kb del) -1/12 (homozygous 7.6 kb del) -1/12 (compound HT 6.7 and 7.6 kb del)

			-All patients had growth failure, very low GH, IGF-1 and IGFBP-3. -MRI showed Hypoplastic Adenohypophysis
17	7.6 kb [27]	Homozygous	-Two Hispanic sisters with short stature and high body fat. -Developed antibodies against rhGH exposure.
18	c.1G>T 7.6 kb [28]	Compound Heterozygous	-A Japanese patient with growth retardation confirmed after provocative GH testing. -Responded well to hGH therapy. -Did not develop anti-hGH antibody
19	6.7 kb or 7.6 kb [29]	Homozygous	-3 Brazilian patients with growth hormone deficiency. -2 patients had 6.7 kb del (developed anti-GH antibodies after therapy) and 1 patient with 7.6 kb del (No anti-GH antibodies developed). -All the 3 patients had common phenotype; large forehead, low nasal bridge, increased subcutaneous fat, thin hair, and a high-pitched voice.

Figure 1. Weight-for-age and Height-for-age growth chart for males aged 0-2years
At the time of recruitment, the patient's weight was 6.80kg (0th percentile, -5.03SDs) indicating that he is severely underweight. The patient has severe short stature with a height of 71cm (0th percentile, -5.4SDs). The mid parental height is 158cm.

Figure 1 Weight-for-age and Height-for-age growth chart for males aged 0-2years

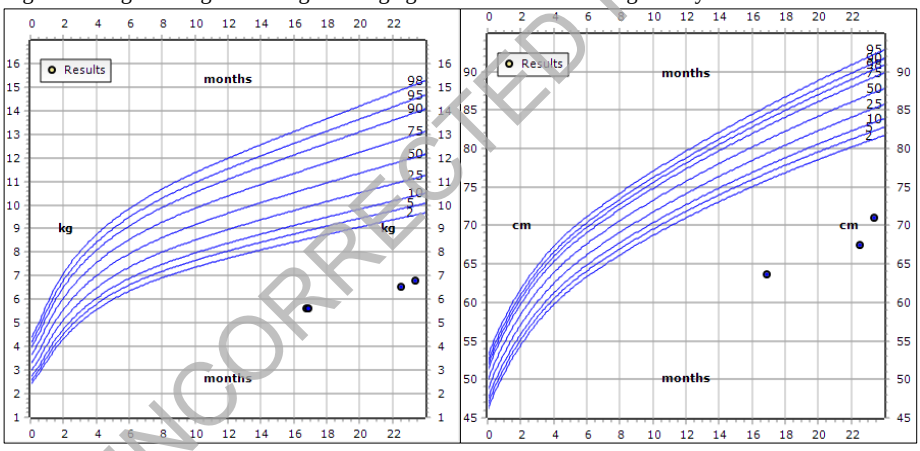

Figure 2. Family pedigree for IGHD Type 1A patient

Figure 2 Family pedigree for IGHD Type 1A patient

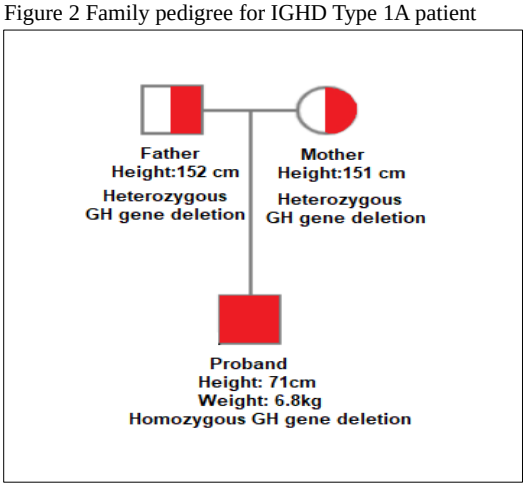

Figure 3. Results of genetic analysis for the patient and parents. a) IGV track showing homozygous 6 kb deletion in the proband (top), heterozygous deletion in both parents (middle) and wild type control (bottom) from the bam-files of the samples. b) Samplot analysis of whole genome sequencing showing structural variant (6 kb deletion spanning the entire GH1 gene on chromosome 17 (GRCh37/hg19 17:61993713-62000168)

Figure 3 Results of genetic analysis for the patient and parents.

Figure 3a IGV track showing homozygous 6 kb deletion in the proband (top), heterozygous deletion in both parents (middle) and wild type control (bottom) from the bam-files of the samples.

Figure 3b Samplot analysis of whole genome sequencing showing structural variant (6 kb deletion spanning the entire GH1 gene on chromosome 17 (GRCh37/hg19 17:61993713-62000168)