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CASE REPORT

# A novel GCM2 mutation identified in an infant with familial isolated hypoparathyroidism

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## ABSTRACT

**Background:** Isolated hypoparathyroidism comprises a set of heterogeneous inherited diseases associated with abnormal calcium metabolism exclusively due to parathyroid hormone (PTH) deficiency. Isolated hypoparathyroidism can be either sporadic or inherited. Genetic causes that impair the synthesis or secretion of PTH, such as calcium-sensing receptor and *PTH* defects, or defects in the development of the parathyroid gland [glial cell missing 2, (*GCM2*)], have been established as causes of familial isolated hypoparathyroidism. Transcription factor *GCM2* is a crucial regulator of parathyroid gland homeostasis. Transmission of pathogenic variants encoding *GCM2* occurs in an autosomal recessive or dominant manner.

**Case Presentation:** Herein, we describe the case of a 12-year-old boy, born to consanguineous parents, who presented with abnormal movement during the first week of birth. Laboratory results revealed hypocalcemia, hyperphosphatemia, and low PTH levels. Genetic testing detected a novel homozygous variant in the *GCM2* gene, c.391C>T (p.Arg131*). Although this variant has not been previously described, it is likely the pathogenic cause of this condition.

**Conclusion:** To the best of authors' knowledge, this variant has not been listed in any database. Proper replacement therapy is likely to have good long-term outcomes for our patient.

**Keywords:** *GCM2*, GCMB, hypoparathyroidism, c.391C>T, *CASR*, case report.

## Introduction

Parathyroid hormone (PTH) is essential for regulating calcium and phosphate homeostasis, acting directly in the bones and kidneys and indirectly in the gastrointestinal tract by regulating the production of renal 1,25 dihydroxy vitamin D (1). Hypoparathyroidism results from a transient or permanent decrease in PTH secretion or action, or dysfunction of the parathyroid gland (1). Hypoparathyroidism can have primary and secondary etiologies, the former of which is due to an intrinsic defect within the parathyroid gland, mostly due to genetic causes. It may be isolated or occurs as a part of a syndrome; isolated hypoparathyroidism can be sporadic or run-in families. Secondary or acquired forms of hypoparathyroidism occur due to the removal or destruction of the parathyroid gland, leading to irreversible damage or vascular compromise (2).

Hypoparathyroidism symptoms are mainly due to hypocalcemia, which leads to long-term mental and physical worsening symptoms such as convulsions, laryngospasm, and deferred disease management. Other symptoms may include fatigue and muscle weakness. Although the onset of familial hypoparathyroidism symptoms usually occurs during infancy, it can occur anytime from birth to adulthood (3). Familial isolated hypoparathyroidism is an uncommon disease associated with calcium metabolism abnormalities and is caused by a deficiency in PTH secretion, without related developmental defects or endocrine disorders. It is transmitted via different modes of inheritance. The autosomal recessive mutations include homozygous inactivating mutations in the *PTH* or glial cell missing

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2 (*GCM2*) genes on chromosome 6p24.2. Autosomal dominant mutations include heterozygous mutations that either inactivate *PTH*, activate the calcium-sensing receptor (*CASR*) gene (4), or gain-of-function mutation of guanine nucleotide binding protein a11 (9).

In this paper, we present a case of familial isolated hypoparathyroidism in a 12-year-old boy and the results of *GCM2* molecular analysis.

## Case Presentation

The patient was a 12-year-old Saudi boy born at full-term (41 weeks gestational age) via spontaneous vaginal delivery, birth weight of 3,065 g (50th-75th percentile), length of 51 cm (50th-75th percentile), and head circumference of 35 cm (25th percentile), according to the Centers for Disease Control and Prevention (CDC) growth chart. Apgar scores were 9 at both 1 and 5 minutes. After the routine newborn screening, the boy was discharged with his mother in good health condition.

He was fed breast and formula milk; on day 4 of life, his mother noticed abnormal movements in the form of up rolling of the eyes and perioral mouth twitching. He was admitted to the hospital, where he was found to have low calcium and high phosphate levels and required intravenous calcium administration. He was diagnosed with hypoparathyroidism and started on alfacalcidol (0.2 mcg twice daily).

The patient was seen in our endocrine clinic at the age of 1 year and 5 months; his weight was 8.4 kg (third percentile) and his height was 77.2 cm (fifth percentile), according to the CDC growth chart. He failed to thrive, was not dysmorphic, and cardiac anomalies were ruled out. Two younger siblings and cousins in the same family had the same clinical history and were receiving calcium supplements; one was also receiving alfacalcidol.

During his subsequent visits to our endocrine clinic, his normal bone profile was maintained. Currently, he is showing excellent academic performance with good intelligence. Although his calcium level dropped to a low level at a time, he was never admitted due to symptomatic hypocalcemia.

### *Family pedigree*

The proband's parents are first-degree consanguine (Figure 1). Two younger affected siblings.

## Investigations

Initial investigations at our hospital showed the following biochemical findings (Table 1): Ca level 1.63 (2.2-2.7) mmol/l, corrected Ca level 1.59 (2.2-2.7) mmol/l, PTH level 5 (15-65) pg/ml, level of 25 hydroxy vitamin D 80.8 (50-150) nmol/l, and urine Ca/Cr ratio 0.64 (0.6-0.74). Chest radiography was normal, but renal ultrasound showed bilateral nephrocalcinosis. Based on clinical presentation and investigation results, he was diagnosed with hypoparathyroidism. He improved clinically and biochemically while being treated with alfacalcidol (0.2 mg twice per day) orally. Molecular genetic analysis of the *CASR* was negative, and a Whole Exome Sequencing (WES) analysis was performed.

The genetic analysis involved the collection of blood samples from the patient for DNA extraction after obtaining written informed consent from the parents. The initial molecular analysis did not detect *CASR*. However, whole-exome sequencing identified a novel homozygous variant of the *GCM2*: c.391C>T (p.Arg131*). As per the American College of Medical Genetics and Genomics recommendations, this variant creates a stop codon and is categorized as a likely pathogenic mutation (Class 2). Our variant was linked to the patient's phenotype as the type of mutation is loss-of-function. The mutation was identified by next-generation sequencing and confirmed via Sanger sequencing in both the forward and reverse directions.

As per VarSome verdict, the variant has been classified pathogenic (PVS1), which suggests very strong evidence of pathogenicity as null variant (nonsense); in *GCM2,* loss-of-function is a known mechanism underlying its pathogenic phenotype. PM2, which suggests moderate pathogenicity based on GnomAD exomes/genome homozygous allele count 0, is less than 3 for AD/AR gene *GCM2*. PP3 suggests supporting pathogenicity based on computational verdict derived from five pathogenic predictions using BayesDel_addAF, DANN, EIGEN, FATHMM-MKL, and MutationTaster versus no benign predictions.

The variant was also detected in a heterozygous state in the proband's parents; since the parents were asymptomatic, we speculate that it was inherited in autosomal recessive mode. Our findings provide evidence that this defect causes decreased parathyroid secretion, resulting in hypocalcemia.

## Discussion

Herein, we report a mutation in *GCM2* as a novel variant of familial isolated hypoparathyroidism in a child presenting with abnormal movement in the neonatal period. Laboratory investigations (Table 1) showed hypocalcemia, hyperphosphatemia, a normal urine Ca/Cr ratio, and low PTH levels. (5) The patient improved dramatically after replacement therapy with oral calcium, followed by alfacalcidol prescription.

*GCM2*, formerly GCMB, is a transcription factor that plays a crucial part in the regulation of parathyroid development and maturation. In humans, *GCM2* is composed of 506 amino acids and is located on chromosome 6p24.23. Homozygous loss-of-function and heterozygous dominant mutations in *GCM2* cause autosomal recessive and autosomal dominant isolated hypoparathyroidism, respectively (9).

Considering the presence of familial hypoparathyroidism, a hereditary disorder was suspected; genetic testing revealed a likely pathogenic variant of *GCM2*. The gene was discovered through extensive research aimed at delineating the causative gene for this disorder in cases with familial isolated hypoparathyroidism.

In a report on *GCM2*-associated familial isolated hypoparathyroidism, Ding et al. (6) described a homozygous biallelic pathogenic variant in their family

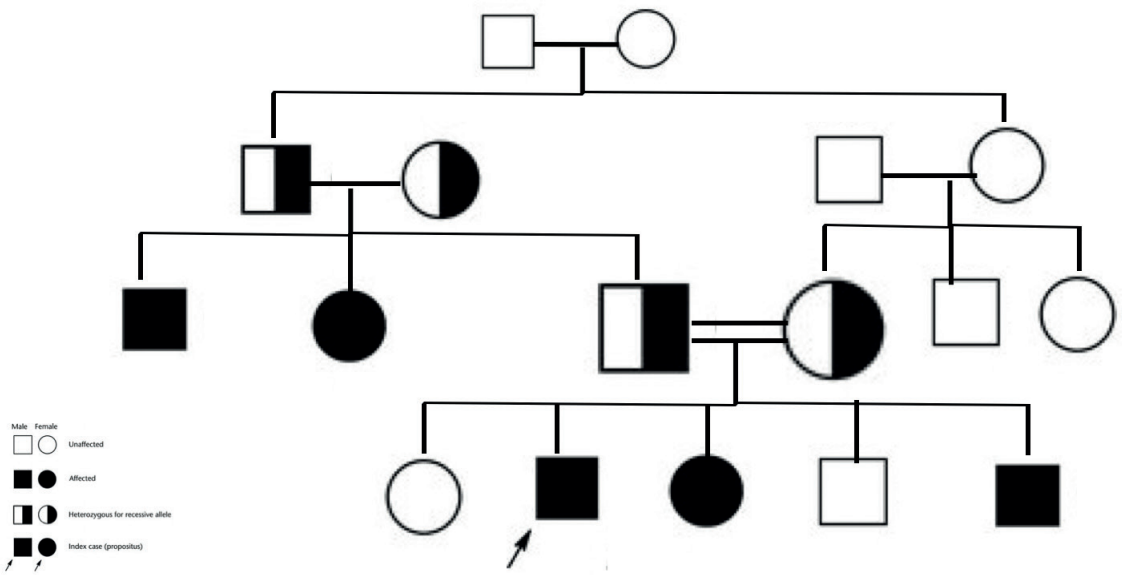


***Figure 1.*** *Family pedigree.*

***Table 1.*** *Clinical characteristics.*

| Variables<br>Age | Results<br>Neonate | Results<br>15 months | Normal reference values |
|---|---|---|---|
| Weight | 3.065 kg | 8.4 kg | - |
| Length/height | 51 cm | 77.2 cm | - |
| Calcium | 1.79 | 1.63 | (1.12-2.57) mmol/l |
| Corrected Ca | - | 1.59 | (2.2-2.7) mmol/l |
| Phosphate | 2.6 | 2.4 | (0.6-1.5) mmol/l |
| PTH | 3 | 5 | (15-65) pg/ml |
| 25 Vitamin D | - | 80.8 | (50-150) nmol/l |
| Urine Ca/Cr ratio | - | 0.64 | (0.6-0.74) |

cohort study. The variant was an exon 4 deletion, and the founder effect was confirmed by haplotype analysis of the cohort. Thus, they concluded that *GCM2* loss-of-function is a causative factor for the disorder (6). Baumber et al. (7) identified a new variant associated with the disorder in members of a Pakistani family, which is a homozygous missense mutation in *GCM2* (R47L). Furthermore, a study by Thomee et al. (8) in an Arab population described a different variant of *GCM2* that was confirmed to be disease-causing in two Moroccan siblings. The gene variant is a homozygous missense mutation (G63S).

## Conclusion

Evidence supports the pathogenicity of the variant identified in the present case. First, both parents were heterozygous and asymptomatic. The variant is expected to result in truncated protein expression (P. arg131*), leading to abnormal function as evident in *in silico* parameters. Additionally, the carrier frequency was <1% (0.00082) (6).

The gene variant described here has not yet been reported in OMIM, PubMed, and VarSome databases so far.

### List of Abbreviations

| | |
|---|---|
| *CASR* | Calcium-sensing receptor |
| *GCM2* | Glial cell missing 2 |
| PTH | Parathyroid hormone |

### Declaration of conflicting interests

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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### Consent for publication

Informed consent was obtained from the parents for the publication of this case report.

### Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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**References**

1. Shoback DM, Bilezikian JP, Costa AG, Dempster D, Dralle, H, Khan AA, et al. Presentation of hypoparathyroidism: etiologies and clinical features. J Clin Endocrinol Metab. 2016;101:2300–12. https://doi.org/10.1210/jc.2015-3909
2. Clarke BL, Brown EM, Collins MT, Jüppner H, Lakatos P, Levine MA, et al. Epidemiology and diagnosis of hypoparathyroidism. J Clin Endocrinol Metab. 2016;101:2284–99. https://doi.org/10.1210/jc.2015-3908
3. Hawkes CP, Al Jubeh JM, Li D, Tucker SE, Rajiyah T, Levine MA. Novel PTH gene mutations causing isolated hypoparathyroidism. J Clin Endocrinol Metab. 2022;15:dgac086. https://doi.org/10.1210/clinem/dgac086
4. Canaff L, Guarnieri V, Kim Y, Wong B, Nolin-Lapalme A, Cole D, et al. Novel glial cells missing-2 (GCM2) variants in parathyroid disorders. Eur J Endocrinol. 2022;186(3):351–66. https://doi.org/10.1530/EJE-21-0433
5. Andersen SL, Frederiksen AL, Rasmussen AB, Madsen M, Christensen AR. Homozygous missense variant of PTH (c.166C>T, p.(Arg56Cys)) as the cause of familial isolated hypoparathyroidism in a three-year-old child. J Pediatr Endocrinol Metab. 2022;35:691–4. https://doi.org/10.1515/jpem-2021-0752
6. Ding C, Buckingham B, Levine MA. Familial isolated hypoparathyroidism caused by a mutation in the gene for the transcription factor GCMB. J Clin Invest. 2001;108:1215–20. https://doi.org/10.1172/JCI200113180
7. Baumber L, Tufarelli C, Patel S, King P, Johnson CA, Maher ER, et al. Identification of a novel mutation disrupting the DNA binding activity of GCM2 in autosomal recessive familial isolated hypoparathyroidism. J Med Genet. 2005;42:443–8. https://doi.org/10.1136/jmg.2004.026898
8. Thomee C, Schubert SW, Parma J, Le PQ, Hashemolhosseini S, Wegner M, et al. GCMB mutation in familial isolated hypoparathyroidism with residual secretion of parathyroid hormone. J Clin Endocrinol Metab. 2005;90:2487–92. https://doi.org/10.1210/jc.2004-2450
9. Cinque L, Sparaneo A, Penta L, Mencarelli A, Rogaia D, Esposito S, et al. Autosomal dominant PTH gene signal sequence mutation in a family with familial isolated hypoparathyroidism. J Clin Endocrinol Metab. 2017;102(11):3961–9. https://doi.org/10.1210/jc.2017-00250