Short stature and hypoparathyroidism in a child with Kenny-Caffey syndrome type 2 due to a novel mutation in FAM111A gene

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Abstract

Background: Hypoparathyroidism in children is a heterogeneous group with diverse genetic etiologies. To aid clinicians in the investigation and management of children with hypoparathyroidism, we describe the phenotype of a 6-year-old child with hypoparathyroidism and short stature diagnosed with Kenny-Caffey syndrome (KCS) Type 2 and the subsequent response to growth hormone (GH) treatment.

Case presentation: The proband presented in the neonatal period with hypocalcemic seizures secondary to hypoparathyroidism. Her phenotype included small hands and feet, hypoplastic and dystrophic nails, hypoplastic mid-face and macrocrania. Postnatal growth was delayed but neurodevelopment was normal. A skeletal survey at 2 years of age was suggestive of KCS Type 2 and genetic testing revealed a novel de novo heterozygous mutation c.1622C > A (p.Ser541Tyr) in FAM111A. At 3 years and 2 months, her height was 80cms (SDS −3.86). She had normal overnight GH levels. GH therapy was commenced at a dose of 4.9 mg/m 2/week for her short stature and low height velocity of 5cms/year. At the end of the first and second years of GH treatment, height velocity was 6.5cms/year and 7.2cms/year, respectively with maximal dose of 7.24 mg/m 2/week.

Conclusion: This case highlights the phenotype and the limited response to GH in a child with genetically proven KCS type 2. Long-term registries monitoring growth outcomes following GH therapy in patients with rare genetic conditions may help guide clinical decisions regarding the use and doses of GH in these conditions.

Keywords: Kenny-Caffey syndrome Type 2, FAM111A gene, Growth hormone, Hypoparathyroidism, Short stature, Genetics

Background

Hypoparathyroidism is an important cause of neonatal hypocalcemia presenting in the first week of life [1]. It is characterized by low or normal parathyroid hormone (PTH) levels in the presence of hypocalcemia and hyperphosphatemia. Although commonly seen as an iatrogenic complication following anterior neck surgery in adults, the etiology of hypoparathyroidism in children is more diverse and includes a heterogeneous group of disorders, many of which have a genetic basis [2, 3]. An increased understanding of the genetic etiology and improved genetic testing has provided an opportunity to expand the molecular diagnosis of hypoparathyroidism [2].

Kenny-Caffey syndrome (KCS) is an uncommon cause of hypoparathyroidism with one out of 37 patients reported with this condition in a cohort of children with primary hypoparathyroidism [3]. It is characterized by proportionate short stature along with cortical thickening and medullary stenosis of tubular bones, delayed closure of anterior fontanelle, eye abnormalities, and hypoparathyroidism. The autosomal dominant form or KCS Type 2 (OMIM 127000) caused by mutations in FAM111A [4] is distinguished from the autosomal recessive form (KCS Type 1), caused by mutations in tubulinfolding cofactor E (TBCE) gene, by the absence of...
microcephaly and mental retardation [5]. Awareness of the different phenotypes and the underlying genetic mutation improves the ability of the physician to undertake appropriate investigations, predict patient outcomes and provide appropriate genetic counselling [3]. We present the clinical characteristics of a 6-year-old girl with neonatal hypocalcaemia, post-natal short stature, macrocrania and normal intellect diagnosed with KCS Type 2.

**Case presentation**

The proband was born by natural conception to non-consanguineous Italian parents at 39 weeks of gestation by an elective caesarean section for breech delivery with a birth weight of 3.26kgs (SDS 0.1), length of 49cms (SDS −0.1) and head circumference of 36cms (SDS 1.8). She presented on day 8 of life with hypocalcemic seizures secondary to hypoparathyroidism (Table 1) with normal blood glucose and renal function. Normocalcemia was achieved with parenteral calcium gluconate infusion. Thereafter, supplementation with oral elemental calcium and calcitriol maintained appropriate serum levels of calcium and phosphate. Her phenotype included macrocrania and large persistent fontanelles. She had relatively elfin facies with hypoplasia of the mid-face, telecanthus, small palpebral fissures, a small pinched upturned nose and a small chin (Fig. 1a and b). Proportionate limb shortening with additional circumferential skin folds was present. Hands and feet were small with bilateral single palmar creases and triangular, hypoplastic and dystrophic nails (Fig. 2). An ophthalmological examination in the neonatal period did not reveal any abnormalities.

Her neurodevelopment was normal. However, linear growth was poor (Fig. 1c) and dentition delayed; her first tooth erupted at 16 months. At 1 year of age, her length was 65.5cms (SDS −3.5) Figs. 3 and 4 demonstrate the height and head circumference respectively. Macrocrania was more pronounced during infancy and plateaued after 2 years of age although the head circumference continued to be disproportionate to the height. There was no family history of short stature, macrocephaly, skeletal and nail deformities or hypoparathyroidism. Parents were clinically unaffected with maternal height of 162.5cms and paternal height of 182.9cms, the predicted mid-parental target height was 166.2cms (SDS 0.4). Figure 5 demonstrates the overnight growth hormone (GH) study [6] performed at 2.6 years of age. It showed a normal GH reserve with a peak of 15 μg/L with serum insulin-like growth factor 1 (IGF-1) of 57 μg/L (SDS −1.9). GH was measured using a solid-phase, two-site chemiluminescent immunoassay on the Immulite 2000 XPI (Siemens Healthcare Diagnostics Inc, Deerfield, IL). IGF-1 was measured by chemiluminescent immunoassay on the automated analyser Diasorin Liaison (Diasorin Inc, Stillwater, MN). At 3 years and 2 months, her height was 80cms (SDS −3.86) (<3rd percentile on WHO growth chart, <1st percentile on CDC growth chart) with a height velocity of 5cms/year. GH treatment was commenced at 3 years and 3 months with a starting dose of 4.9 mg/m²/week (0.2 mg/kg/week) [7], under the Pharmaceutical Benefits Scheme Growth Hormone Program for ‘Short stature and slow growth’ [8]. This category utilises the following auxological parameters on the CDC growth charts; height <1st percentile on the CDC growth chart and low height velocity (<3rd percentile CDC growth chart). There were no side effects and good compliance with administration of injections was maintained.

**Table 1** Laboratory investigations with neonatal hypocalcaemia

| Investigations       | Patient values | Normal values |
|----------------------|----------------|---------------|
| Serum calcium        | 1.15           | 2.15–2.75 mmol/l |
| Ionised calcium      | 0.72           | 1.1–1.4 mmol/l  |
| Serum phosphate      | 4.07           | 1.4–2.6 mmol/l  |
| Serum magnesium      | 0.47           | 0.7–1.1 mmol/l  |
| Albumin              | 37             | 25–40gm/L      |
| PTH                  | <0.3           | 0.7–7pmol/l    |
| Alkaline phosphatase | 251            | 100–420u/l     |
| Vitamin D            | 98             | >50 nmol/l     |

**Investigations:** Initial investigations included a normal echocardiogram, renal ultrasound and MRI brain. There was also a persistent normocytic anaemia with haemoglobin of 95gm/L (NR: 110–145) with normal iron stores and haemoglobin electrophoresis. Karyotype and FISH for 22q11.2 deletion were normal. There was no pathogenic variant demonstrated on CASR, PTH and GCMB gene analysis. Chromosomal microarray revealed a small paternally inherited micro-duplication of chromosome 17p13.2 not known to cause any of the described phenotypic features. The proband’s father is asymptomatic, not dysmorphic and has normal calcium and PTH levels. A skeletal survey performed in the neonatal period was inconclusive; however, the repeat survey at 2 years of age was suggestive of KCS with overtubulated long bones, metacarpals and metatarsals with very little medullary space as shown in Fig. 6. The anterior fontanelle was widely patent with multiple Wormian bones. Further genetic testing revealed a novel de novo heterozygous mutation c.1622C > A (p. Ser541Tyr) in FAM111A. This genetic variant was predicted to be probably damaging by PolyPhen (score 0.99) [9], deleterious by SIFT (score 0.0) [10] and damaging by FATHMM (score −3.50) [11] suggesting that the mutation may be damaging. Furthermore, this variant is not present in the ExAC [12], 1000 Genomes
Project [13], and NHLBI GO Exome Sequencing Project databases [14], supporting the putative dominant effect of this mutation. The variant lies in the peptidase domain of **FAM111A**, where a pathogenic variant for KCS type 2 was previously identified [4, 15] as shown in Fig. 7.

**Follow-up:** Hypoparathyroidism was treated with oral calcium and calcitriol supplementation. Apart from early echogenic changes in the renal pelvis at 2 years of age, there has been no evidence of nephrocalcinosis or nephrolithiasis on follow-up at 4.6 years of age with normal renal function and urinary calcium excretion.

Figure 3 demonstrates the response to GH treatment. After the first year of GH treatment on 4.9 mg/m²/week (0.2 mg/kg/week), her height was 86.9 cms (SDS −3.7), with a height velocity of 6.5 cms/year. Serum IGF-1 levels increased from 52 μg/L (−1.9 SDS) to 154 μg/L (−0.2 SDS) during this period. The GH dose was increased to 6.23 mg/m²/week with a corresponding increase in IGF-1 to 193 μg/L (0.45 SDS) with further increment of doses (7.24 mg/m²/week or 0.33 mg/kg/week) in the next eight months. Her height velocity was 7.2 cms/year at the end of second year of treatment with serum IGF-1 of 128 μg/L (−0.63 SDS). At 5.11 years, her weight is 14 kgs and height is 98.9 cms (SDS −3.18).

**Conclusions**
The case highlights the clinical characteristics in a child with KCS Type 2 due to a novel **FAM111A** mutation. Hypoparathyroidism was diagnosed in the neonatal period and near normocalcemia was achieved with calcium and calcitriol supplements. Investigations ruled out the more commonly encountered DiGeorge syndrome and mutations in the less common **PTH** and **CASR** genes affecting PTH secretion, and **GCMB** gene related to parathyroid embryogenesis. Our proband did not have genetic confirmation of her condition until 4 years of age. We considered the diagnosis of KCS Type 2 based on her clinical and radiological features. The neonatal skeletal survey was inconclusive; however, a survey repeated at 2 years of age raised the
possibility of KCS with the evidence of medullary stenosis. She had additional features including macrocrania with widely separated sutures, dysmorphic features, normal intellect and developmental milestones. The absence of intellectual impairment and microcephaly excluded KCS Type 1 and Sanjad Sakati syndrome. The genetic cause of KCS Type 2 was first reported by Unger et al., and involves the “Family with sequence similarity 111, member A00 (FAM111A) gene (NM_001142519.1)” as reported in five patients with KCS Type 2 and five patients with severe osteocranios tenosis (OCS) [4]. KCS type 2 and OCS were allelic disorders of different severity with each having a close genotype-phenotype correlation. The p.Arg569His (R569H) mutation was consistently associated with the KCS phenotype while another mutation, p.Ser342del, was associated with the lethal phenotype of OCS. Japanese researchers also identified the same mutation independently in another four patients and they concluded that R569H is a hot spot mutation for KCS Type 2 [15]. Our proband has a novel FAM111A mutation (p. Ser541Tyr), which lies in the same peptidase domain as the hot spot mutation. Within this domain, the S541 residue, along with H385, and D439 forms the putative catalytic triad of FAM111A [4]. As a consequence, the mutation in our proband may impair the catalytic activity of FAM111A. The identified cases from the two above-mentioned series were de novo mutations [4, 15]. However, the earliest description of KCS described a mother-to-son transmission [16] and
Fig. 4 Figure 4 shows the head circumference of the patient
this has been further elaborated in a second case of mother-to-daughter transmission of the same mutation with both mother and child affected [17] consistent with an autosomal dominant inheritance.

**FAM111A** has very low overall sequence identity to known proteins; however, the second half of the protein has homology to a family of peptidases (IPR009003). We generated a 3D protein model of **FAM111A** (Fig. 5b and c) using a known protease with the highest sequence similarity to **FAM111A** (SWISS-MODEL template ID 4ic6.1) [18]. The S541 residue appears to lie closer to the core of the protein, consistent with its predicted role as part of the catalytic triad (Fig. 5b) whereas the R569 residue appears to be on the outer surface of the protein (Fig. 5c), as previously reported by Unger and colleagues [4]. Furthermore, our functional predictions of Ser541-Tyr suggest that the variant may have very damaging effects, in contrast to the tolerated and benign predictions made on Arg569His [9]. Taken together, the pathogenicity of the novel **FAM111A** mutation in our proband may be different to the previously identified hot spot mutation.

**FAM111A** is constitutively expressed in bone and parathyroid gland and may have a role affecting intracellular pathways regulating normal bone development, height gain, and parathyroid gland development and/or

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**Fig. 5** Figure 5 shows the overnight growth hormone (GH) test. Blood sample is collected every 20 min for GH and the physiological surge in GH is profiled. GH levels during waking hours are normally low. During sleep, there are usually several pulses of GH >20 mU/L (7.7 μg/L), usually associated with slow wave sleep. A peak GH response <10 mU/L (3.9 μg/L) suggests GH deficiency; a response of 10–20 mU/L (3.9–7.7 μg/L) may suggest partial GH deficiency; a response >20 mU/L (>7.7 μg/L) is regarded as normal. (1 mU/L × 0.385 = 1 μg/L)

**Fig. 6** Figure 6 **a** shows relatively poor ossification of skull vault, patent metopic suture, widely separated sagittal sutures on anteroposterior view of X-ray Skull. Figure 6 **b** shows tubulated long bones with reduced medullary space and cortical thickening on anteroposterior view X-ray Tibia.
regulation [4, 15]; although the precise mechanisms are unknown. *FAM111A* demonstrates nuclear localization and interacts with the C-terminal of SV40 large T antigen to promote viral replication in a transfected human osteosarcoma cell line (U2OS) [19]. Studies evaluating chromatin during DNA replication have identified interaction between *FAM111A* and proliferating cell nuclear antigen, a key part of the complex involved in stabilization of DNA polymerases during replication [20, 21]. Depletion of *FAM111A* in U2OS cells resulted in delayed entry into S-phase and DNA synthesis [19]. The interaction of GH signalling with *FAM111A* function either directly or indirectly in utero and postnatally is not yet elucidated. This will be an important area of future investigation.

Patients with *FAM111A* mutations have severe short stature (−3 to −7 SDS) [4]. KCS has been identified as a cause for short stature with dysmorphic features in the absence of hypoparathyroidism [22]. Our proband did not exhibit prenatal growth restriction and growth faltered in the first year of life. This is similar to the other reported cases and hence it suggests that *FAM111A* is predominantly involved with postnatal growth [9]. The slow growth in our proband was striking in the absence of dietary issues, coeliac disease or any other chronic illness. The anaemia, although persistent, was mild and hence unlikely to contribute to the severity of growth restriction observed in our patient. She was eligible for GH therapy under the ‘Short stature and slow growth’ category in Australia [8]. We initiated GH therapy at 3 years and 3 months of age with the intention of improving final height despite normal constitutive GH levels. There has been one other report of the use of GH (dose unspecified) in a female patient with KCS Type 2 in whom GH was commenced at 3.6 years for short stature [22, 23]. An initial response in growth velocity was not sustained in the latter patient and therapy was changed over to IGF-1 therapy, which was subsequently discontinued due to severe headaches, poor compliance and poor growth response. Reintroduction of GH treatment improved her growth velocity. The height SDS improved from −5.99 at baseline to −3.38 at 12 years and 1 month [22]. In our patient, there was reportedly good compliance to treatment throughout therapy and the height SDS improved from −3.86 to −3.18. During her first year of treatment, the height velocity of 6.5 cm/year was below −1 SDS on the Bakker’s curve [24]. The GH dose of 4.5 mg/m²/week (0.17 mg/kg/week) is the standard dose used for commencement of GH therapy in Australia; this is lower than that used in other countries (0.3 mg/kg/week). There was an improvement in height velocity in the second year of treatment as the GH dose...
increased, although the response remained suboptimal even after therapy increased to 0.3 mg/kg/week as demonstrated in Fig. 3. It is not known if doses above 0.3 mg/kg/week would have been effective at improving growth velocity, as she was not eligible for higher GH doses at the time of her treatment under the Australian Growth Hormone Programme funded by the Pharmaceutical Benefits Scheme.

Many children with genetic and syndromic conditions are eligible for GH therapy under the category of ‘Short stature and slow growth’ in Australia. This group forms the largest category of patients treated with GH during childhood. In an observational study (1990–2013) of the Australian Growth Hormone Programme, rates of non-compliance approached 50% and early cessation of GH treatment was noted [24]. The expense of treatment [25] and the unknown long-term effects increase the complexity of management [26] of patients with short stature. Normal variation in height extends beyond the growth hormone-insulin-like growth factor 1 (GH-IGF-1) axis [27]. Short stature in KCS Type 2 is not due to perturbation of the GH-IGF-1 axis and is likely to be associated with a skeletal defect that limits growth. Recent advances in sequencing have enabled more rapid identification of the genetic etiology in children with short stature and support newer diagnostic and therapeutic paradigms centred on understanding the genetics of the growth plate and skeletal development [27]. These may enable better targeting of GH treatment in children with short stature. Case reports such as these provide important information for families and raise the issue of the prioritization and costs of genetic tests prior to GH therapy for short stature.

Although limited to a single case, this report aims to provide clinicians with information regarding growth response of KCS Type 2 with GH therapy. We propose that clinical case reports such as ours and collaborations between clinicians to establish and support international registries monitoring and reporting the outcome of GH therapy in rare genetic conditions such as KCS would be helpful in moving towards personalise medicine and guiding clinical decisions about the use and doses of GH in short stature.

Abbreviations
GH: Growth hormone; IGF-1: Insulin-like growth factor 1; KCS: Kenny-Caffey syndrome; OCS: Osteocraniostenosis; PTH: Parathyroid hormone; SDS: Standard deviation score

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Authors’ contributions
MBA collated clinical information of the case and wrote the manuscript. DL, HH and MAL provided the genetic diagnosis and expert opinion, SMO provided clinical details, FM provided initial genetic analyses, and EML provided expert biochemical opinion. DT performed the bioinformatic analyses. CSC oversaw all aspects of the manuscript and edited the manuscript. All authors reviewed and approved of the final version of the manuscript. Part of this work was presented at the 8th APPES Biennial Scientific Meeting, Darwin, Australia 2014 and published online in IPE. Abraham et al. International Journal of Pediatric Endocrinology 2015, 2015 (Suppl 1):P72. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Written informed consent was obtained from the parents of the patient for publication of this case report and the accompanying images, according to the Princess Margaret Hospital Human Research Ethics Committee procedures.

Ethics approval and consent to participate
Not applicable.

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