Clinical Report

Mother and daughter with Kenny-Caffey syndrome: the adult phenotype

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ARTICLE INFO	ABSTRACT
Handling Editor: A. Verloes	Kenny-Caffey Syndrome (KCS) is a genetic syndrome characterized by growth retardation with short stature, cortical thickening and medullary stenosis of long bones, and hypoparathyroidism with hypocalcemia. KCS and the related but more severe condition osteocraniostenosis are determined by monoallelic variants in the *FAM111A* gene. Here we describe the KCS phenotype resulting from the monoallelic *FAM111A* variant p.Y511H in a 31-year-old woman and in her 56-year-old mother, who is one of the oldest affected individuals known so far. To our knowledge, it is also one of the few molecularly confirmed cases of a mother-to-child transmission of KCS.

1. Introduction

In 1966, Kenny and Linarelli described a boy and his mother who were both affected by short stature ("dwarfism"), hypocalcemia, and cortical thickening of tubular bones (Kenny and Linarelli, 1966). Shortly thereafter, Caffey described the radiographic features in more detail (Caffey J et al., 1967). The condition has since been known as Kenny-Caffey syndrome; it is mostly sporadic but has dominant transmission and, as in the original family, has been documented multiple times.

In 1988, Sanjad, Sakati and Abu-Osba described a different condition characterized by short stature, hypoparathyroidism with hypocalcemia, dysmorphic features, intellectual disability, and autosomal recessive inheritance (Sanjad SA et al., 1988). Richardson and Kirk described the same syndrome in 1990 as "short stature, mental retardation and hypoparathyroidism" (Richardson and Kirk, 1990). It later became known as "Sanjad-Sakati syndrome" (Kelly TE et al., 2000). This condition, more commonly found in individuals of Arabian origin, is caused by biallelic variants in the *TBCE* gene (Parvari R et al., 2002).

The two conditions are listed as (dominant) *FAM111A*-related Kenny-Caffey syndrome and (recessive) *TBCE*-related Sanjad-Sakati syndrome in the most recent nosology of genetic disorders of bone (Unger S et al., 2023); OMIM still lists Sanjad-Sakati syndrome as "KCS type 1" and the original, dominantly-inherited Kenny-Caffey syndrome as "KCS type 2"; this highlights the necessity of systematically applying

the dyadic naming convention (Unger S et al., 2023). KCS is clinically characterized by short stature, delayed closure of fontanels, cortical thickening of the long bones and medullary stenosis, hypermetropism/hyperopia, dental abnormalities, and primary hypoparathyroidism with chronic or episodic hypocalcemia that can lead to seizures and/or tetany; intelligence is not affected (Isojima T et al., 2014; Nikkel SM et al., 2014). It is an autosomal dominant syndrome due to a heterozygous variant in *FAM111A*, a gene that seems significant for parathyroid hormone regulation, calcium homeostasis, and bone development (Unger S et al., 2013). Almost all of the confirmed KCS patients described in literature had de novo variants in *FAM111A*, and only a few cases of parent-to-child transmission have been described (Kenny and Linarelli, 1966; Nikkel SM et al., 2014; Schigt H et al., 2023). To the best of our knowledge, only 35 patients with a confirmed KCS diagnosis are described in literature, and the phenotypic spectrum is mostly described in the pediatric population. The natural history of this condition is still unknown: the oldest KCS patients described to date are a woman of 56 years of age (Ohmachi Y et al., 2023), and a man, died at 77 years of age with a clinical diagnosis of KCS, which had three children with a KCS clinical and molecular diagnosis (Schigt H et al., 2023). Here we describe the adult phenotype of a 31-year-old woman and her 56-year-old mother, who is also one of the oldest KCS patients reported thus far in literature.

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2. Patient data Patient 1

Patient 1, the proband, was delivered at 34 weeks gestation as a result of an intrauterine growth restriction with a birth weight of 1750 g (−1 SD) and a length of 39 cm (−2 SD). Head circumference not available. The psychomotor development was normal. At 4 years old, she was referred to clinicians for poor growth, hypocalcemia (with normal parathyroid hormone), scleral icterus, high levels of transaminases, and a delayed closure of the anterior fontanel. She underwent treatment with growth hormone (GH) therapy from 5 to 14 years old. In 2001, at the age of 12, the diagnosis of KCS was formulated based on her clinical and radiological features. Radiographs performed during infancy were unavailable. Menarche was at 14 years old, then menses were irregular with oligomenorrhea, leading to a diagnosis of polycystic ovary syndrome associated with excess weight and impaired glucose tolerance. She also began hormone replacement therapy for a diagnosis of hypothyroidism. A pelvic ultrasound, abdomen ultrasound, hearing examination, echocardiogram and karyotype were all normal. An MRI of the dorsal spine detected a right convex scoliosis. She had hyperopia and needed corrective glasses. A brain CT in 2014 detected symmetrical calcification in the basal nuclei but was interpreted as a marker without a pathological significance at the time.

At the genetic evaluation performed in our medical genetics clinic, we observed the following anthropometric parameters in the 31-year-old proband: stature of 138 cm (−4 SD), head circumference of 50.5 cm (−2.5 SD), and an arm span of 139 cm with an upper segment to lower segment ratio of 1.12. Dysmorphic features included sparse hair, prominent frontal bossing and a high frontal hairline, midface hypoplasia, small palpebral fissures, low set ears, and prognathism (Fig. 1A). Long bone X-rays showed the classic findings of KCS with cortical thickening and medullary stenosis of tubular bones (Fig. 2).

3. Patient data Patient 2

Patient 2, the proband's mother, was evaluated at our medical genetics clinic at the age of 56. Prenatal and perinatal information about Patient 2 was unavailable. She had her first hypocalcemic clonic seizure at 17 days of life and was subsequently given a diagnosis of hypoparathyroidism. Height and weight gain were always poor. In 1964, a karyotype was performed showing a mosaicism for Turner syndrome (mos 45,X/46,XX); however, the report of the genetic test was unavailable. In 2016, she was referred to clinicians for an episode of loss of consciousness, with the EEG showing a right hemispheric irritative activity with a central-parietal focus. Antiepileptic therapy was started. A brain CT showed conspicuous parenchymal calcifications both supra- and subtentorial on both sides. A brain MRI detected a diffuse hypersignal of the periventricular supratentorial white matter and dentate nucleus and a marked hyposignal in basal nuclei, interpreted as calcium or hemosiderin deposits. Her daughter referred a progressive loss of motor autonomy due to instability beginning approximately 3 years ago, which has resulted in her to using a wheelchair. Other medical issues include oligodontia, glaucoma, sensorineural hearing loss, and chronic kidney disease (CKD). On physical examination, stature was 126 cm (−5 SD) and head circumference was 48.5 cm (−3.5 SD). Her arm span was 130 cm with an upper segment to lower segment ratio of 1.11. Dysmorphic features included sparse hair, high frontal hairline, midface hypoplasia, small palpebral fissures, and a pointed chin (Fig. 1B). Radiographs of Patient 2 were not available.

4. Methods

Blood samples from both patients were collected. Chromosomal karyotype in the mother was performed: a hundred metaphases were analyzed, 97 metaphases were normal (46,XX) and in three metaphases a monosomy of chromosome X was detected (3%).

After DNA extraction, both samples were submitted for Sanger

Fig. 1. A) Physical features of Patient 1. B) Physical features of Patient 2.

sequencing of the coding exons (exon 4 and exon 5) of the *FAM111A* (NM_001312909) gene. PCR primers were designed and are described in the Supplementary Table. The coding sequence of exon 5 was completely covered by using five pairs of primers. PCR fragments were purified and directly sequenced in both strands using the ABI BigDye Terminator v3.1 Cycle Sequencing Kit and the ABI 3500 DNA Analyzer (Applied Biosystems, Foster City, CA, USA). Sequencing analysis in both mother and daughter identified the heterozygous missense variation c.1531T > C corresponding to p.(Tyr511His) [Y511H] in exon 5 (DECIPHER patient ID 532294). This missense variation has already been described in literature (Unger S et al., 2013) and confirmed the clinical diagnosis of KCS.

5. Discussion

KCS is a genetic primary skeletal dysplasia due to *FAM111A* mutations and characterized by growth retardation with short stature, delayed closure of the anterior fontanel, and cortical thickening and medullary stenosis of the long bones. Another characteristic of this condition is hypoparathyroidism, which can cause, both in early childhood and adulthood, hypocalcemia and, consequently, convulsions. In addition, macrocephaly, dysmorphic features, calcifications of the basal
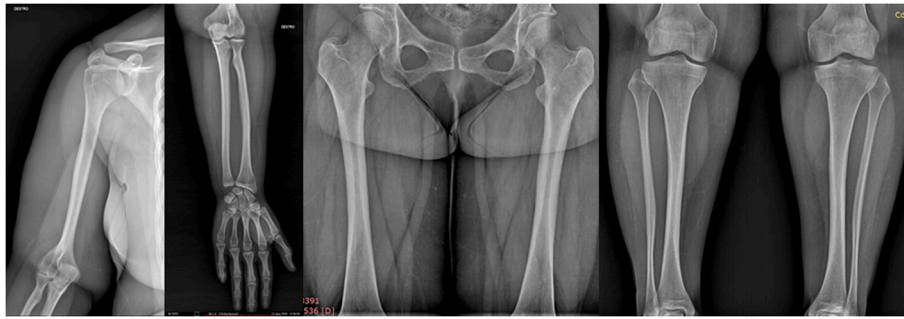
Fig. 2. Radiographs of Patient 1 at 31 years old. Upper limbs, pelvis, and lower limbs show cortical thickening and medullary stenosis of tubular bones.

nuclei detected by neuroimaging, dental abnormalities (tooth agenesis, edentulism, delayed dentition, premature shedding of permanent dentition, severe caries), and ocular defects (microphthalmia, hypermetropia, astigmatism) may be present (Cheng SSW et al., 2020; Deconte D et al., 2020; Yerawar C et al., 2021; Isojima T et al., 2014; Schigt H et al., 2023). The psychomotor development is usually normal. Currently, most of the KCS patients described in literature are pediatric cases, and few reports have been reported on the phenotype in adulthood. Our case report highlights the clinical characteristics in a 31-year-old woman and her 56-year-old mother with a diagnosis of KCS due to *FAM111A* mutation. The mother, to our knowledge, is one of the oldest KCS patients reported thus far in literature. Her phenotypic spectrum shows classic clinical features of skeletal dysplasia and hypoparathyroidism with additional sensorineural hearing loss, CKD, and a progressive motor impairment with loss of walking ability associated with parenchymal calcifications detected by neuroimaging. Recently, Ohmachi Y et al. described a 56-year-old woman with KCS with hypoparathyroidism, short stature, cortical thickening and medullary stenosis of the bones, calcification of the capsule at the brain CT, hyperuricemia from age 24 years, bilateral sensorineural hearing loss at 49 years, lumbar spondylolisthesis, and vestibular dysfunction (Ohmachi Y et al., 2023).

Sensorineural hearing loss has been described in five KCS adult patients thus far (Kenny and Linarelli, 1966; Unger S et al., 2013; Nikkel SM et al., 2014; Ohmachi Y et al., 2023; Schigt H et al., 2023), while vestibular dysfunction has been reported only by Ohmachi Y et al. Patient 2 shows progressive loss of motor autonomy due to instability, but vestibular function tests have never been performed.

In addition to our Patient 2, Schigt H et al. described six other KCS adult patients with CKD or kidney transplantation: in all patients no cause for CKD was found other than the hypothesis of the possibly natural KCS course or the related treatment, including vitamin D and calcium supplements, as no nephrocalcinosis or hypercalciuria were detected (Schigt H et al., 2023). Previously, nephrocalcinosis had been reported in four KCS patients as the main renal disease (Cavole TR et al., 2020; Cheng SSW et al., 2020). CKD has never been associated with KCS before, most likely because the previously described patients with KCS were in infancy; this information could be significant because it suggests that KCS patients may have an increased risk of developing CKD in adulthood.

FAM111A is located in the long arm of chromosome 11 (11q12.1) and encodes for a serine protease, which contains four main domains: a PCNA (proliferating cell nuclear antigen) Interacting Peptide (PIP) box, two ubiquitin-like domains (UBL-1 and UBL-2), and a C-terminal Trypsin 2-like serine protease domain (Welter and Machida, 2022). Fine et al. found that the serine protease domain of *FAM111A* interacts with the C-terminal domain of SV40 Large T antigen (LT) and functions through an antiviral defense mechanism (Fine DA et al., 2012). Recently, *FAM111A* was also found to have a role in DNA replication, acting at the DNA replication fork through its interaction with PCNA (Welter and Machida, 2022). However, the role of *FAM111A* in KCS has

not yet been clarified. Recent studies demonstrated that *FAM111A* mutations in KCS are gain-of-function mutations that lead to reduced DNA synthesis, disruption of nuclear structure, and cell death due to dysregulated protease activity of *FAM111A* (Hoffmann S et al., 2020; Nie M et al., 2021). *FAM111A* is constitutively expressed in bone and in parathyroid glands and may have a role affecting intracellular pathways regulating normal bone development, height gain, and parathyroid gland development and/or regulation (Unger S et al., 2013; Isojima T et al., 2014). The c.1531T > C (Y511H) variant in *FAM111A* that was detected in our patients has been previously described only once by Unger et al. in a 7-year-old patient with short stature, delayed closure of fontanels, and dental anomalies (Unger S et al., 2013), and it is absent from the major genomic databases (ExAc, GnomAD, EVS, and 1000Genome). To our knowledge, we are also reporting one of the molecularly confirmed cases of a mother-to-child transmission of KCS: a mother-to-child transmission was at the origins of Kenny and Caffey's first report and Nikkel et al. also documented a mother-to-daughter transmission in 2014 (Kenny and Linarelli, 1966; Nikkel SM et al., 2014). Kenny et al. described a mother (39 years) and her son (3 years) with a similar clinical phenotype: poor growth, hypocalcemia, myopia, delayed closure of the anterior fontanel, cortical thickening and medullary stenosis of the bones. In the mother hearing defect and oligodontia were also reported (Kenny and Linarelli, 1966).

It is currently assumed that KCS males were subfertile or infertile because of microorchidism and micropenis (Cheng SSW et al., 2020; Hoffman WH et al., 1998; and personal observation by ASF); however, Schigt et al. have reported the first instance of paternal transmission of KCS (Schigt H et al., 2023). It is possible that the *FAM111A* variant in that family, p.Glu535Gly, may have resulted in an attenuated clinical phenotype allowing for male fertility.

To date, about 35 genetically confirmed KCS patients with a clear phenotypic description have been reported. Most of them are in infancy and thus have a short-term follow-up (Cheng SSW et al., 2020). The mechanisms of *FAM111A* mutations, protein regulatory pathways, and the disease's natural history will be a significant area of future investigation. Information about the phenotypic spectrum of KCS is still limited and a better understanding of the natural history, especially for KCS adult clinical features, will be important for clinical management.

Disclosure statement

The authors have no conflicts of interest to declare.

Statement of ethics

The patients have given written informed consent for the use of clinical information and pictures in this report.

CRediT authorship contribution statement

L. Tonelli: Conceptualization, Visualization, Writing – original draft. **M. Sanchini:** Conceptualization, Visualization. **A. Margutti:** Investigation, Methodology, Resources, Validation. **B. Buldrini:** Investigation, Methodology, Resources, Validation. **A. Superti-Furga:** Supervision, Writing – review & editing. **A. Ferlini:** Visualization, Writing – review & editing. **R. Selvatici:** Conceptualization, Visualization, Writing – original draft. **S. Bigoni:** Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing.

Data availability

I have shared data at the Attach File step (Manuscript and Supplementary Material).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2024.104943.

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