(International Print/Online Journal)

SJIF IMPACT FACTOR: 6.829
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 9, Issue 3, Page No: 509-511
May-June 2026

IJMSCR

Small Body, Seizing Brain; Cracking The Fam111a Code In Kenny Caffey Syndrome

Sairaj Salgar[1], Prithi Inamdar[1], Ankitha Ponathil[1], Pooja Vora[1]
[1]Department of Pediatrics, Dr. D Y Patil Hospital, Nerul, Navi Mumbai

***Corresponding Author:**
Dr. Sairaj Salgar
Department of Pediatrics, Dr. D Y Patil School of Medicine, Nerul, Navi Mumbai

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Kenny-Caffey Syndrome Type 2 is a rare autosomal dominant disorder caused by heterozygous mutations in the FAM111A gene, characterized by proportionate short stature, cortical thickening of long bones, hypoparathyroidism, and dysmorphic facies. We report a 7-year-old female born of a non-consanguineous marriage who presented with seizures since 6 months of age, global developmental delay, feeding difficulties, and proportionate short stature. Examination revealed dysmorphic features including frontal bossing, hypertelorism, depressed nasal bridge, and skeletal anomalies. Anthropometry showed height 90 cm and weight 13 kg, both below 3rd centile. MRI brain revealed moderate paucity of cerebral white matter with T2/FLAIR hyperintensities in bilateral frontoparietal subcortical and periventricular regions, suggestive of periventricular leukomalacia. Whole exome sequencing identified a heterozygous missense variant in exon 6 of FAM111A, classified as a variant of uncertain significance but consistent with the phenotype. This case highlights the importance of considering KCS Type 2 in children with short stature, skeletal dysplasia, and neurodevelopmental delay. Early genetic diagnosis enables multidisciplinary management including calcium monitoring, seizure control, and developmental support.

Keywords: Kenny-Caffey Syndrome Type 2, FAM111A, Short stature, Hypocalcemia, Periventricular leukomalacia, Skeletal dysplasia

Introduction

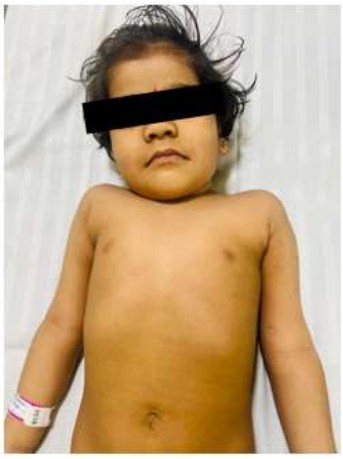
Kenny-Caffey Syndrome is a rare genetic disorder of bone growth and calcium metabolism first described in 1966. Two genetic forms are recognized: Type 1 caused by biallelic mutations in the TBCE gene with autosomal recessive inheritance, and Type 2 caused by heterozygous mutations in the FAM111A gene with autosomal dominant inheritance. KCS Type 2 is characterized by proportionate short stature, medullary stenosis and cortical thickening of long bones, delayed closure of anterior fontanelle, basal ganglia calcification, ocular abnormalities, hypoparathyroidism with hypocalcemia, and dysmorphic facies. Neurological involvement including developmental delay and seizures is increasingly recognized. Due to its rarity and phenotypic overlap with other skeletal dysplasias, diagnosis is often delayed. We present a case of KCS Type 2 confirmed by whole exome sequencing, with associated periventricular leukomalacia on neuroimaging.

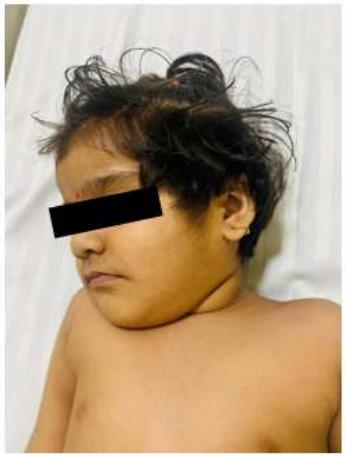
Case Presentation:

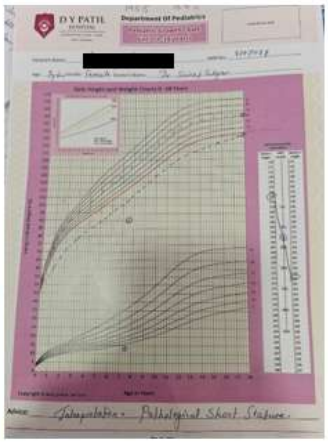
A 7-year-old female child, first born of a non-consanguineous marriage with uneventful antenatal and perinatal history, presented with seizures since 6 months of age, global developmental delay, short stature, and feeding difficulties.

Clinical Examination: Dysmorphic facies noted including frontal bossing, hypertelorism, depressed nasal bridge, deep-set eyes, long philtrum, thin upper lip. Skeletal findings included short clavicles and broad thorax. Anthropometry: height 90 cm (<3rd

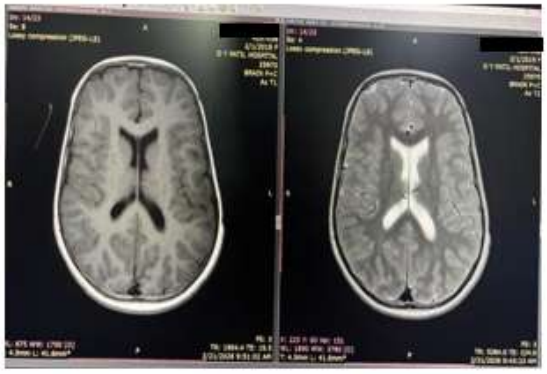
centile, -4.2 SD), weight 13 kg (<3rd centile, -3.8 SD), head circumference 48 cm. Neurological examination revealed generalized hypotonia with gross motor and language delay. No cataracts or dental anomalies were noted.

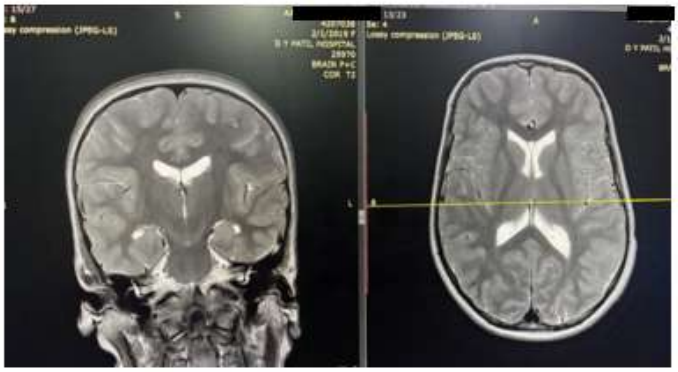






Investigation: MRI brain demonstrated moderate paucity of cerebral white matter with subtle T2/FLAIR hyperintensities involving bilateral frontoparietal subcortical and periventricular white matter, suggestive of periventricular leukomalacia. Ophthalmology and hearing evaluation werje normal.





Genetic Analysis: Whole exome sequencing revealed a heterozygous missense variant in exon 6 of the FAM111A gene. The variant was classified as a variant of uncertain significance per ACMG criteria PM2, but considered clinically relevant given the strong phenotypic match with KCS Type 2. Parental testing was not available.

METROPOLIS

Whole Exome Sequencing

RESULTS

A variant of uncertain significance detected related to the clinical Phenotype

PRIMARY FINDINGS

Gene and Transcript	Exon/Intron Number	Variant Nomenclature	Vaf	Variant Type	ACMG criteria	Classification	Zygosity	OMIM Phenotype	Inheritance
FAM111A (NM_001312905.2)	Exon 6/Exon 6	c.3220>T p.Val408Leu [Ste /3034]	49.5%	missense_variant	PM2_M	Uncertain significance	Heterozygous	Kenny-Caffey syndrome, type 2	Autosomal dominant

Volume 9, Issue 3; May-June 2026; Page No 509-511

Management: The child was started on oral calcium and multivitamin supplementation. Antiepileptics were optimized for seizure control. Multidisciplinary care including physiotherapy, occupational therapy, and speech therapy was initiated. Genetic counseling was provided to the family.

Discussion

KCS Type 2 results from gain-of-function mutations in FAM111A, a gene encoding a protein involved in DNA replication and repair. The phenotypic spectrum includes craniofacial dysmorphism, skeletal abnormalities, hypocalcemia due to hypoparathyroidism, and neurodevelopmental issues. Our patient demonstrated classical features of short stature, dysmorphism, skeletal findings, and hypocalcemia.

The presence of periventricular leukomalacia on MRI is noteworthy. While basal ganglia calcification is described in KCS, white matter involvement is less commonly reported. This may contribute to the hypotonia and developmental delay seen in our patient and expands the neurological phenotype of KCS Type 2. Differential diagnoses considered included Sanjad-Sakati syndrome, hypoparathyroidism-retardation-dysmorphism syndrome, and other forms of microcephalic osteo-dysplastic primordial dwarfism, but were excluded based on genetic testing.

Whole exome sequencing was pivotal in establishing the diagnosis, as clinical features alone overlap with multiple syndromes. The identified FAM111A variant, though classified as VUS, is likely pathogenic given the specific phenotype and absence in population databases. This underscores the importance of correlating genetic results with clinical findings in rare disorders.

Management of KCS Type 2 requires a multidisciplinary approach. Key aspects include: 1) Monitoring and treatment of hypocalcemia to prevent seizures and tetany, while avoiding hypercalciuria and nephrocalcinosis; 2) Growth monitoring, though growth hormone therapy has limited role; 3) Neurological and developmental support; 4) Genetic counseling regarding autosomal dominant inheritance and 50% recurrence risk.

Conclusion:

This case underscores the significance of precision diagnostics in rare genetic disorders presenting with short stature and neurodevelopmental delay. Recognition of the clinical spectrum of Kenny-Caffey Syndrome Type 2, supported by molecular confirmation, enables timely intervention and comprehensive care. Neuroimaging findings of periventricular leukomalacia may represent an under-recognized feature of KCS Type 2. Early diagnosis, seizure control, supportive therapies, and regular monitoring of growth, calcium levels, and neurodevelopment are essential for improving long-term outcomes. A multidisciplinary approach and genetic counseling are vital for family support and recurrence risk assessment.

References

1. Unger S, Górna MW, Le Béchec A, et al. FAM111A mutations result in hypoparathyroidism and impaired skeletal development in Kenny-Caffey syndrome type 2. Am J Hum Genet. 2013;92(6):990-995.
2. Isojima T, Doi K, Mitsui J, et al. A recurrent de novo FAM111A mutation causes Kenny-Caffey syndrome type 2. J Bone Miner Res. 2014;29(4):992-998.
3. Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: 127000: Kenny-Caffey Syndrome, Type 2.
4. National Center for Biotechnology Information. FAM111A-related disorders. In: GeneReviews®. Seattle: University of Washington; 1993–2024

Volume 9, Issue 3; May-June 2026; Page No 509-511