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Prenatal diagnosis and management in a case of Kenny-Caffey Syndrome

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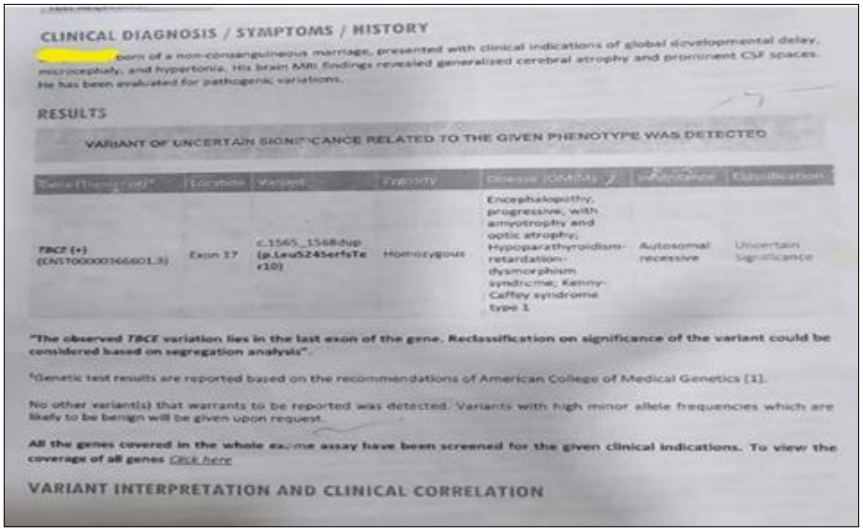
Abstract
Background: Kenny-Caffey syndrome is a rare genetic disorder characterised by short stature, dysmorphic features, and bone abnormalities. A significant number of individuals with Kenny-Caffey syndrome also experience global developmental delay, particularly those with Kenny-Caffey syndrome type 1.
Case Presentation: A 32-year-old lady G4P1L0A2 with a nonconsanguineous marriage visited us with a history of a previous baby who had died at 1.5 years of age. The baby had facial dysmorphism, microcephaly, micrognathia, dental abnormalities, and an electrolyte imbalance of calcium and phosphorus due to hypoparathyroidism. In whole-exome sequencing (WES), a variant of uncertain significance was identified in Exon 17 of the TBCE gene. The couple was also tested and found to be heterozygous for the tested gene mutation.
Intervention/Outcome: In the present pregnancy, the couple was counselled for 25% risk of the condition in the foetus of Kenny-Caffey syndrome. At 12 weeks after the NT NB scan, chorionic villus sampling was performed, and the sample was sent for FISH and targeted mutation analysis of the TBCE gene.
The result was positive for the heterozygous form in the foetus, and the pregnancy was thereafter monitored as a regular antenatal pregnancy. Full term healthy baby was born.
Conclusion/Clinical Significance: Kenny-Caffey Syndrome is a rare genetic disorder that can significantly impact the life of a newborn, with global developmental delay being a notable feature in some cases. Hence, a prenatal diagnosis can help women who have had a prior child with global developmental delay and a subsequent diagnosis of KCS. Identification of the responsible mutation may prevent the occurrence of this syndrome in future pregnancies through carrier detection.

Keywords: Kenny-Caffey Syndrome, global developmental delay, TBCE Gene mutation, Next Generation Sequencing

Introduction
Kenny–Caffey syndrome is a rare genetic disorder characterized by proportionate dwarfism, cortical thickening of tubular bones, dysmorphic features, and hypocalcemia secondary to hypoparathyroidism. The condition was first clinically described by Kenny and Linarelli [1], and its characteristic radiological features were later detailed by Caffey [2]. Two genetic forms have been identified: an autosomal recessive type (KCS1) caused by mutations in the *TBCE* gene, (3) and an autosomal dominant type (KCS2) caused by mutations in the FAM111A gene on chromosome 11q12(4). The molecular basis of the disorder involves pathogenic variants in either the tubulin-specific chaperone E gene (*TBCE*), which is associated with KCS1 (OMIM #244460), or the family with sequence similarity 111-member A gene (FAM111A), which is associated with KCS2 (OMIM #127000) (3), (4)
Functionally, *TBCE* plays an essential role in microtubule assembly and stability, whereas *FAM111A* is implicated in DNA replication and cellular protein processing. We report a rare case of prenatal genetic diagnosis of Kenny–Caffey syndrome in a high-risk pregnancy and discuss its implications for antenatal management.

History
A 32-year-old pregnant woman, gravida 4 para 1 living 0 abortion 2 (G4 P1 L0 A2), presented in early pregnancy with a history of a previous child affected by Kenny-Caffey syndrome who had died at 14 months of age (Figure I). The previous child had global developmental delay, microcephaly, hypertonia, refractory seizures, and aspiration episodes. MRI of the brain had shown generalized cerebral atrophy with prominent cerebrospinal fluid spaces. The couple had a non-consanguineous marriage and no significant family history of genetic disorders.

Fig 1: Case Profile



CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

born of a non-consanguineous marriage, presented with clinical indications of global developmental delay, microcephaly, and hypertonia. His brain MRI findings revealed generalized cerebral atrophy and prominent CSF spaces. He has been evaluated for pathogenic variations.

RESULTS

VARIANT OF UNCERTAIN SIGNIFICANCE RELATED TO THE GIVEN PHENOTYPE WAS DETECTED

Gene (Transcript id)*	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
TBCE (+) (ENST00000366601.3)	Exon 17	c.1565_1568dup (p.Leu524SerfsTer10)	Homozygous	Encephalopathy, progressive, with amyotrophy and optic atrophy; Hypoparathyroidism-retardation-dysmorphism syndrome; Kenny-Caffey syndrome type 1	Autosomal recessive	Uncertain Significance

"The observed *TBCE* variation lies in the last exon of the gene. Reclassification on significance of the variant could be considered based on segregation analysis".

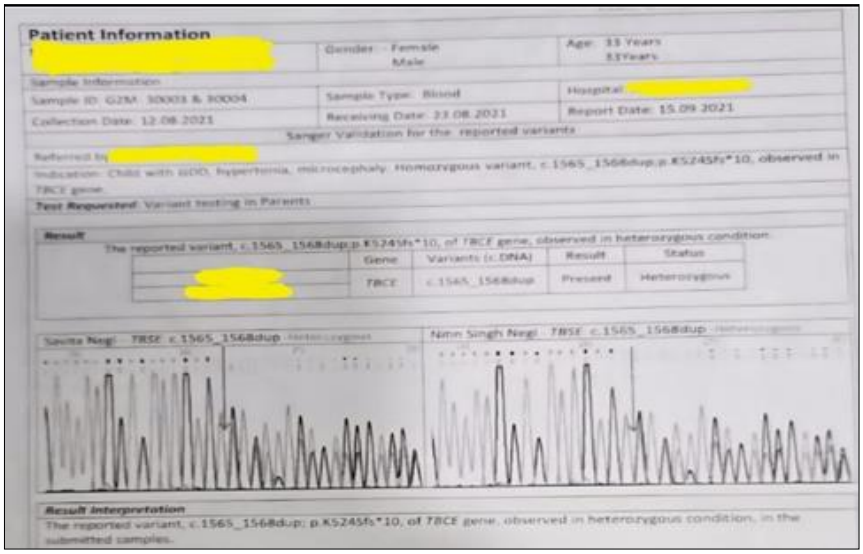
*Genetic test results are reported based on the recommendations of American College of Medical Genetics [1].

No other variant(s) that warrants to be reported was detected. Variants with high minor allele frequencies which are likely to be benign will be given upon request.

All the genes covered in the whole exome assay have been screened for the given clinical indications. To view the coverage of all genes *Click here*

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Fig 2 a: Result of Whole Exome sequencing for the baby post mortem



Patient Information

Gender : Female / Male

Age: 33 Years / 33Years

Sample Information

Sample ID: G2M 30003 & 30004

Sample Type: Blood

Hospital:

Collection Date: 12.08.2021

Receiving Date: 23.08.2021

Report Date: 15.09.2021

Sanger Validation for the reported variants

Referred by:

Indication: Child with GDD, hypertonia, microcephaly. Homozygous variant, c.1565_1568dup,p.K524Sfs*10, observed in *TBCE* gene.

Test Requested: Variant testing in Parents

Result

The reported variant, c.1565_1568dup,p.K524Sfs*10, of *TBCE* gene, observed in heterozygous condition.

Gene	Variants (c.DNA)	Result	Status
TBCE	c.1565_1568dup	Present	Heterozygous

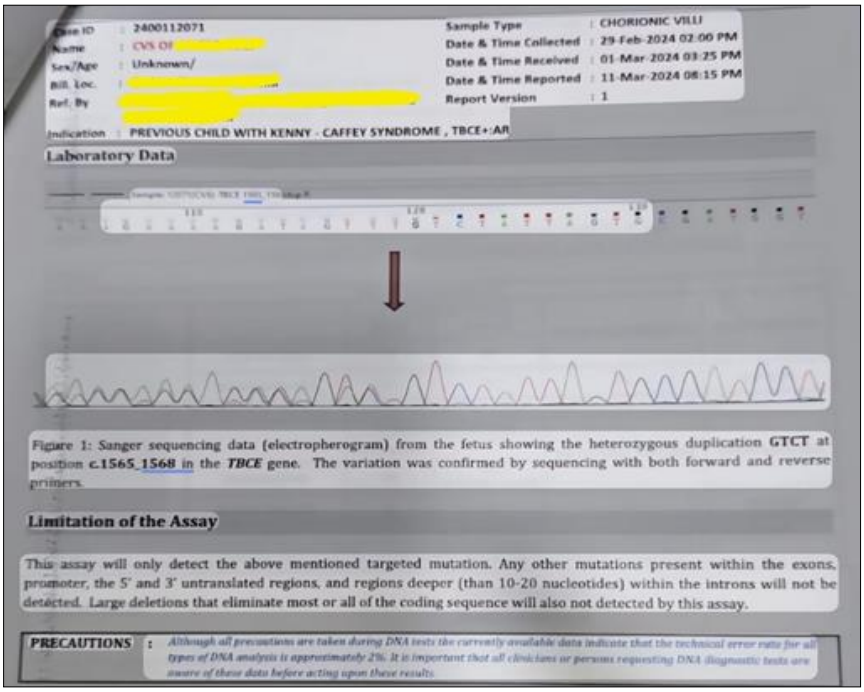
Savita Negi *TBSE* c.1565_1568dup

Nimi Singh Negi *TBSE* c.1565_1568dup

Result Interpretation

The reported variant, c.1565_1568dup; p.K524Sfs*10, of *TBCE* gene, observed in heterozygous condition, in the submitted samples.

Fig 2 b: Sanger sequencing of the couple



Case ID : 2400112071

Name : CVS Of

Sex/Age : Unknown/

Bill. Loc. :

Ref. By :

Sample Type : CHORIONIC VILLI

Date & Time Collected : 29-Feb-2024 02:00 PM

Date & Time Received : 01-Mar-2024 03:25 PM

Date & Time Reported : 11-Mar-2024 08:15 PM

Report Version : 1

Indication : PREVIOUS CHILD WITH KENNY - CAFFEY SYNDROME , TBCE+:AR

Laboratory Data

Figure 1: Sanger sequencing data (electropherogram) from the fetus showing the heterozygous duplication **GTCT** at position **c.1565_1568** in the ***TBCE*** gene. The variation was confirmed by sequencing with both forward and reverse primers.

Limitation of the Assay

This assay will only detect the above mentioned targeted mutation. Any other mutations present within the exons, promoter, the 5' and 3' untranslated regions, and regions deeper (than 10-20 nucleotides) within the introns will not be detected. Large deletions that eliminate most or all of the coding sequence will also not detected by this assay.

PRECAUTIONS : *Although all precautions are taken during DNA tests the currently available data indicate that the technical error rate for all types of DNA analysis is approximately 2%. It is important that all clinicians or persons requesting DNA diagnostic tests are aware of these data before acting upon these results.*

Fig 2 c: Sanger sequencing data from the CVS of the foetus of the present pregnancy

Examination
General physical and obstetric examination at presentation were within normal limits. No dysmorphic features or systemic abnormalities were noted in the mother. Routine antenatal evaluation was unremarkable (Figure II).

Investigations
Post-mortem next-generation sequencing of the previous child identified a homozygous variant (c.1565_1568dup; p. Leu524SerfsTer10) in the TBCE gene (Figure IIa), classified as a variant of uncertain significance. Parental testing showed that both parents were heterozygous carriers of the same mutation (Figure IIb).
In the current pregnancy, a first-trimester scan including nuchal translucency and nasal bone assessment at 12 weeks showed normal findings. Chorionic villus sampling (CVS) was performed under continuous ultrasound guidance. Targeted mutation analysis of the TBCE gene detected the same variant in the fetus in a heterozygous state. Subsequent chromosomal analysis revealed a normal karyotype (Figure IIc).

Intervention
The couple received detailed genetic counselling regarding the 25% recurrence risk of Kenny-Caffey syndrome in each pregnancy. After discussion of diagnostic options, CVS with targeted mutation analysis was planned and performed. Following results confirming carrier status without disease expression, routine antenatal care and surveillance were continued.

Outcome
The pregnancy progressed without complications. A full-term male infant was delivered vaginally. Postnatal evaluation, including cranial ultrasound, abdominal ultrasound, and echocardiography, showed normal findings. The neonate demonstrated no clinical features suggestive of Kenny-Caffey syndrome.

Discussion
Kenny-Caffey syndrome (KCS) is an extremely rare genetic disorder characterized by growth retardation, cortical thickening of long bones, dysmorphic features, and hypocalcaemia due to hypoparathyroidism. The condition was first described clinically by Kenny and Linarelli and later radiologically characterized by Caffey (1). Two genetically distinct forms have been described: the autosomal recessive type (KCS1), caused by mutations in the *TBCE* gene, and the autosomal dominant type (KCS2), associated with *FAM111A* mutations. (2)(3) Because of its rarity and phenotypic overlap with other skeletal dysplasias and syndromic dwarfism conditions, establishing an accurate diagnosis can be challenging.
The present case highlights the importance of a detailed evaluation of the affected proband to enable precise genetic counselling for subsequent pregnancies. Identification of the causative mutation in the previous child allowed targeted testing in the current pregnancy, thereby avoiding diagnostic uncertainty. Such an approach is particularly valuable in rare monogenic disorders where prenatal ultrasonography alone may not detect subtle or early phenotypic manifestations.
Sanjad–Sakati syndrome, which shares overlapping clinical and molecular features with KCS1 and is also linked to mutations in the *TBCE* gene region on chromosome 1q42–q43, should be considered in the differential diagnosis. (4) These entities may represent variable phenotypic expressions of related molecular defects, further emphasizing the role of molecular confirmation.
Prenatal diagnosis through chorionic villus sampling with targeted mutation analysis remains the most reliable method for early detection when a familial mutation is known. In this case, demonstrating a heterozygous state in the fetus excluded disease expression and allowed continuation of the pregnancy with reassurance. This underscores the clinical utility of molecular diagnostics in guiding reproductive decision-making and reducing parental anxiety.
Although therapeutic options for affected individuals are limited, early genetic diagnosis has significant implications for prognosis, counselling, and future family planning. Advances in genomic technologies, including next-generation sequencing and multigene panels, have improved diagnostic accuracy and are increasingly accessible. Molecular studies have demonstrated that *TBCE* plays a key role in microtubule assembly, while *FAM111A* is involved in DNA replication and cellular protein processing, supporting their pathogenic relevance in skeletal and developmental abnormalities. (5). However, these tools must be interpreted cautiously within a clinical context to avoid misclassification of variants.
Overall, this case illustrates that precise molecular characterization of rare inherited disorders enables targeted prenatal diagnosis, informed counselling, and optimized obstetric management. Early identification of pathogenic variants can significantly improve reproductive planning and clinical outcomes for families at risk.

Conclusion
Early molecular diagnosis plays a pivotal role in the management of rare genetic disorders such as Kenny–Caffey syndrome. Identification of the causative mutation in an affected child enables accurate genetic counselling and allows targeted prenatal testing in subsequent pregnancies. In the present case, detection of a heterozygous fetal genotype through chorionic villus sampling excluded disease expression and permitted continuation of pregnancy with reassurance. This case highlights the clinical value of integrating genetic analysis with prenatal diagnostic strategies to guide reproductive decision-making, reduce parental anxiety, and optimize obstetric outcomes in high-risk families.

Declarations
Ethics Approval and Consent to Participate
Ethical approval was waived by the institutional ethics committee because this is a single-case report without identifiable patient information.

Patient Consent for Publication
Written informed consent was obtained from the patient for publication of this case report and accompanying clinical data/images.

Availability of Data and Materials
All relevant clinical data supporting the findings of this case are included within the article. No additional datasets were generated.

Funding
No funding was received for this study.

Conflict of Interest
The authors declare no conflicts of interest.

Author Contributions
All authors contributed to the conception, clinical management, data collection, drafting, and final approval of the manuscript.

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