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ORIGINAL RESEARCH

Exome Sequencing Analysis and Clinical Features of a Chinese Patient with 3M Syndrome and A Review of Literature

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Background: 3M syndrome is a rare autosomal recessive genetic disorder characterized by significant intrauterine and postnatal growth restriction. There is limited research on its genetic basis within the Chinese population.

Methods: We performed trio-based whole-exome sequencing to identify the pathogenic gene in the affected child and collected and organized clinical and imaging data. Relevant information was reviewed through a literature search.

Results: In this study, we present a case involving prenatal diagnostic abnormalities and postnatal confirmation of 3M syndrome, including detailed documentation of clinical features and associated genetic variants. Notably, during prenatal ultrasound examination, the fetus exhibited increased nuchal translucency (NT) and delayed limb development. Postnatally, whole-exome sequencing revealed the compound heterozygous mutations in the CUL7 gene: c.3646–2A>G and c.3355+5G>A. The splicing mutation c.3646–2A>G is a novel pathogenic mutation, while the c.3355+5G>A mutation has been previously reported. In-silico analysis predicted strong pathogenicity for both splicing mutations. Through follow-up, we observed that the patient's height and weight are below the first percentile, with abnormal skeletal development and distinctive facial features. Based on literature review of reported cases, these mutations disrupt the normal function of CUL7-OBSL1-CCDC8 complex in the ubiquitin-proteasome pathway, leading to impaired growth regulation.

Discussion: This study identified a novel splicing mutation in the CUL7 gene in a patient with 3M syndrome, expanding the genetic spectrum of this disorder and contributing novel insights for clinical diagnosis and management.

Keywords: 3M syndrome, CUL7, whole-exome sequencing

Introduction

3M syndrome (OMIM #273750, 612,921, 614205) is a rare autosomal recessive genetic disorder characterized by skeletal linear growth anomaly.[1] Affected individuals experience intrauterine growth restriction and present postnatally with short stature, distinctive facial features, tubular and elongated bones, and elevated vertebral bodies. Notably, this disorder does not involve intellectual disability or damage to other organs.[2] First identified and reported by geneticists MuKusick, Malvaux, and Miller, in 1975, the syndrome was named after their initials.[3] To date, approximately 200 cases have been reported in the literature worldwide (Table S1–S3), with only a limited number of cases documented in Chinese reports.[4]

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The molecular mechanism of 3M syndrome was first clarified in 2005 by Huber et al, who identified pathogenic mutations in the CUL7 gene in a cohort of 3M syndrome patients.[5] Subsequent investigations have expanded our understanding, identifying that OBSL1 (Obscurin-Like 1) and CCDC8 (Coiled-coil domain containing 8, also known as P90) are also associated with 3M syndrome. Among these, CUL7 is the most common causative gene, responsible for 3M syndrome 1, with a mutation prevalence ranging from 56% to 77.5%. OBSL1 mutations contribute to 3M syndrome 2, with a prevalence of 16.3% to 44%. In contrast, CCDC8 mutations are rare and correspond to 3M syndrome 3.[6]

In this study, we present a case of 3M syndrome in an infant. Whole-exome sequencing was utilized to validate the diagnosis and revealed a previously unreported variant in the CUL7 gene, enriching the molecular landscape of this syndrome within the Chinese population.

Methods

Study Design

The study included a patient diagnosed with 3M syndrome who was treated at the Second Affiliated Hospital of Wenzhou Medical University. Whole-exome sequencing analysis was performed on blood-derived DNA from both the patient and their parents. This article outlines the clinical features and potential genetic mechanisms of this case, while also reviewing the genetic mechanisms and potential pathogenic loci associated with 3M syndrome as reported in previous studies.

Patients and Samples

This study focused on a case of a 3M syndrome patient, a male infant who was admitted to the Second Affiliated Hospital of Wenzhou Medical University. Basic information, including initial diagnosis age, clinical manifestations, and physical examinations, was collected through the electronic medical records system. Informed consent for genetic research was obtained from the parents or caregivers. The study protocol received approval from the Ethics Committee of Yuying Children's Hospital at Wenzhou Medical University (2023-K-148-01), and the research adheres to the principles of the Declaration of Helsinki.

Whole-Exome Sequencing (WES)

At the Second Affiliated Hospital of Wenzhou Medical University, a child with 3M syndrome was enrolled. Peripheral blood samples were collected from the affected child and their parents. Subsequently, comprehensive whole-exome sequencing was performed on the blood-derived DNA. The genomic DNA underwent random fragmentation, followed by purification. Whole-genome exome capture was then conducted to prepare the sequencing library. An Illumina HiSeqXTen sequencer performed double-ended high-throughput sequencing with a fragment length of 150 bp.

Variant Analysis

The sequences were aligned to the human reference sequence (NCBI Genome build GRCh37) using the Burrows–Wheeler Aligner. The Genome Analysis Toolkit pipeline was employed for the identification of single-nucleotide variants (SNVs) and indels (20644199). Variants were annotated utilizing the RefSeq hg19 gene definitions and external databases through ANNOVAR (20601685). We conducted gene function prediction utilizing various software tools, including SIFT, CADD, Mutation Taster and SpliceAI, subsequently compared clinical symptoms. Finally, we searched relevant disease databases and references to identify potential gene mutation sites for family verification. The variant annotation databases employed encompassed Human Genome hg19/GRCh37, RefSeq, dbSNP, 1000 Genomes Phase3, ExAC, and gnomAD.

Co-Segregation Test

Genetic modifications arising from mutations were identified in both the probands and their parents. Primers were specifically designed for sequencing synthetic DNA fragments based on exome sequencing data from the mutation site. PCR was employed to amplify DNA from both probands and their parents. Sanger sequencing was then utilized for

sequencing. Subsequently, sequencing results were compared with those obtained from whole-exome sequencing to identify any discrepancies.

Results

Clinical Presentation of a Patient with 3M Syndrome

The patient's parents are in a non-consanguineous marriage and both are in good health. At 12 weeks and 4 days of gestation, a routine early pregnancy ultrasound screening revealed an increased nuchal translucency (NT) of 5.4mm, indicating NT thickening (Figure 1). A subsequent primary systemic ultrasound at 16 weeks and 4 days indicated that the fetal size was within the normal range, with an abdominal circumference of 123 mm, the biparietal diameter of 37 mm and the femur length of 20 mm. However, a prenatal ultrasound at 30 weeks and 3 days showed that both femur and humerus lengths were >4 SD below the mean for gestational age, and the abdominal circumference was >2 SD below the mean. These findings collectively indicated a fetal size equivalent to 28 weeks and 2 days. At 37 weeks and 2 days of gestation, a prenatal diagnostic ultrasound examination revealed that the fetal femur length was consistent with 29 weeks of gestation, while the humerus length matched that of 26 weeks of gestation (Figure 2). The patient was born at full term with a birth weight of 2140g, which was below the 10th percentile for fetal weight at the same gestational age.

The patient is currently 11 months old, with a height of 61 cm, weight of 5.8 kg, and head circumference of 41 cm, all below the first percentile for age. Additionally, the child has distinctive facial features including a triangular face, broad forehead, and low nasal bridge (Figure 3A). Skeletal abnormalities are evident, with a prominent sternum creating a pigeon chest appearance, small vertebrae with reduced anteroposterior diameter, and narrowing of the vertebral arch roots from L1 to L5. The iliac bones are slightly square-shaped; both radii and ulnae show mild enlargement at the metaphyses with irregular, slightly flared margins; both femora and tibiae also exhibit metaphyseal enlargement with irregular margins and slight deformity, with the upper segments of the tibiae slightly tilted; the phalanges are slightly short and thick, resembling bullet shapes (Figure 3B–H). The child's intellectual development is normal. These clinical features are consistent with the presentation of 3M syndrome.

Gene Mutation Identified Through Whole-Exome Sequencing

After birth, a blood sample was obtained from the patient for molecular genetic analysis, revealing a compound heterozygous mutation in CUL7 (c.3646–2A>G and c.3355+5G>A). Sanger sequencing validated these mutations, and it was found that they originated from the patient's healthy parents (Figure 4). The c.3355+5G>A mutation has been previously reported in the literature, with studies indicating that this splicing mutation results in an addition of 19 nucleotides in exon 17. However, the c.3646–2A>G splicing mutation was not identified in the normal control population

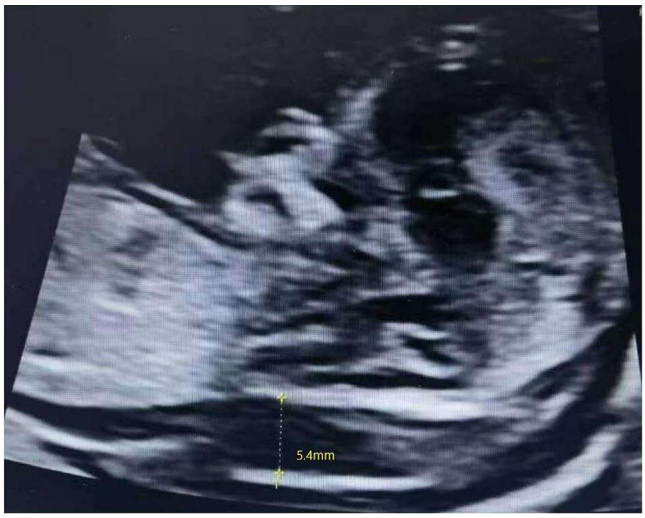

Figure 1 The fetal ultrasound examination of patient's nuchal translucency. The NT thickness is 5.40 mm at 12 weeks and 4 days gestation.

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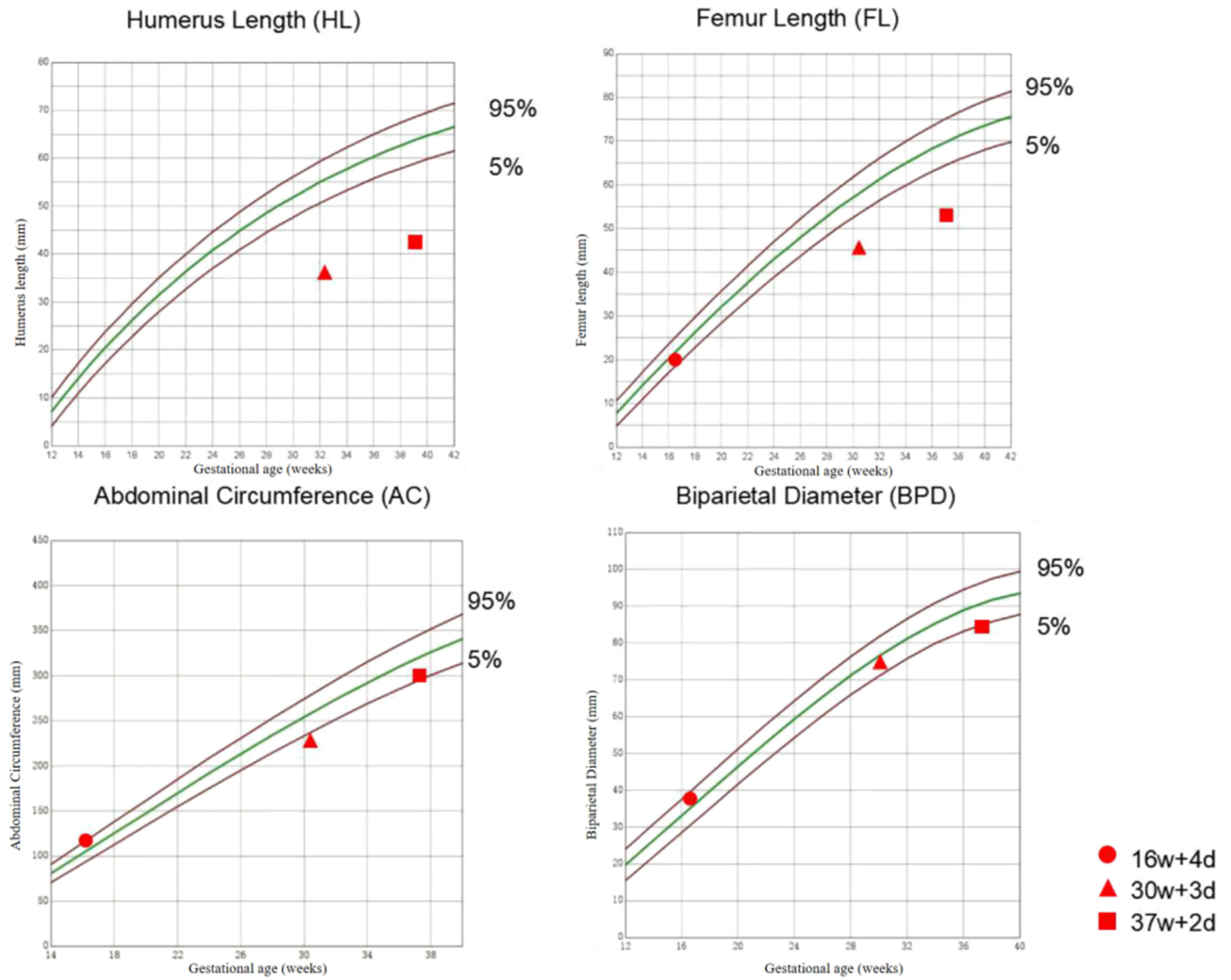

Figure 2 The fetal ultrasound 2D measurements. At 16+4 weeks of gestation, the abdominal circumference was 123 mm, the biparietal diameter was 37 mm and the femur length was 20 mm. At 30+3 weeks of gestation, the abdominal circumference was 233 mm, the biparietal diameter was 74 mm, the humerus length was 38mm, the femur length was 45 mm. At 37+2 weeks of gestation, the abdominal circumference was 301 mm, the biparietal diameter was 84 mm, the humerus length was 45mm, the femur length was 53 mm.

of the Thousand Genomes database, Exome Sequencing Project (ESP) database, the Exome Aggregation Consortium (EXAC) database and Genome Aggregation Database (GnomAD). Furthermore, nucleic acid conservation predictions suggested a high level of conservation for this splicing mutation. Software predictions classified this splicing mutation as pathogenic (Table 1).

Genetic Mechanism of 3M Syndrome

CUL7

Cullins constitute a structurally related protein family with varied cellular regulatory functions.[5] CUL7 interacts with other cellular proteins (SKP1, FBXW8, and ROC1) to assemble an E3 ubiquitin ligase complex, thereby facilitating ubiquitination. Ubiquitination is a pivotal cellular process involving tagging of intracellular proteins for degradation by the 26S proteasome. It is crucial for the normal functioning of many vital biological processes, including cell cycle progression, cell proliferation, apoptosis, and signal transduction pathways.[7]

Huber et al identified the first causative gene for 3-M syndrome.[5] In their study involving 29 pedigrees affected by 3M syndrome, they found 25 distinct mutations in the CUL7 gene. The researchers confirmed the correlation between

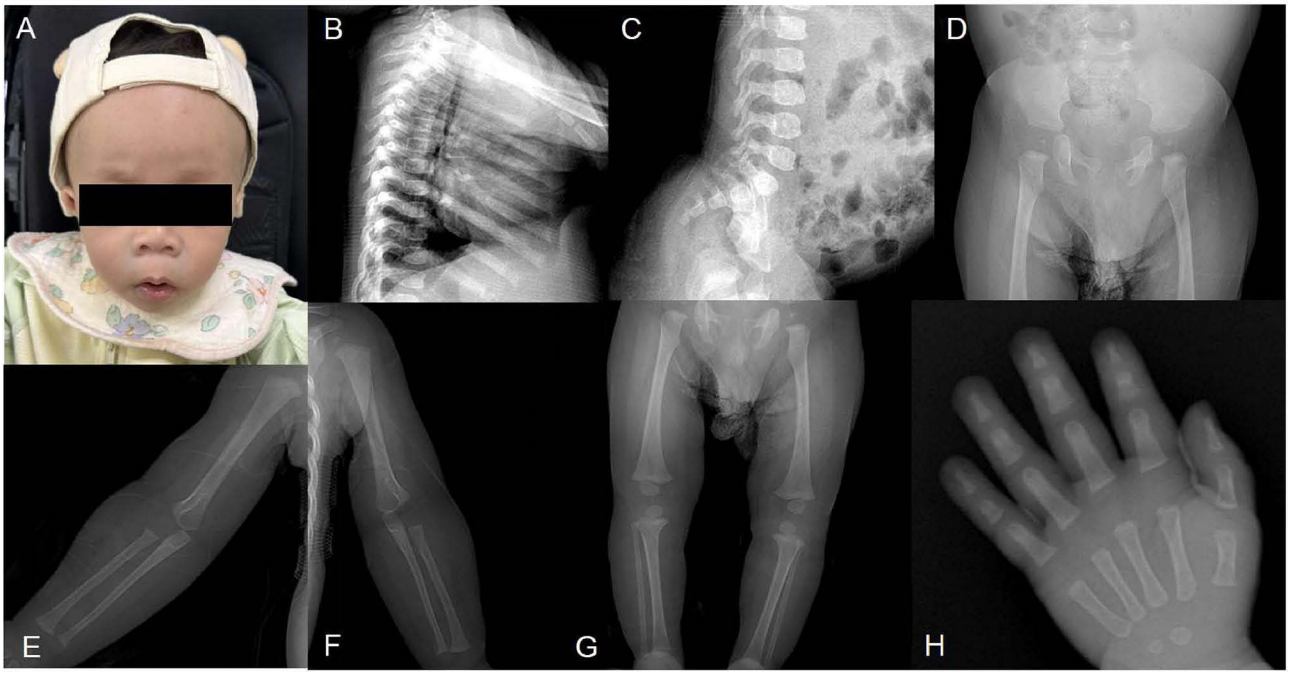

Figure 3 The patient's facial appearance and radiographic images. (**A**) The patient has distinctive facial features, such as a triangular face and a broad forehead. (**B**) The lateral chest radiograph shows anterior sternal protrusion with corresponding changes in the anterior ribs and costal cartilages on both sides. (**C**) The lateral lumbar spine radiograph indicates that the vertebral bodies are small with a reduced anteroposterior diameter, and the interpedicular distances progressively decrease from L1 to L5. (**D**) The pelvic radiograph shows slight squaring of the iliac bones, shortened iliac bases, flattened acetabula, and irregular femoral head morphology. (**E** and **F**) The full-length anteroposterior radiograph of the upper limbs indicates slight enlargement of the metaphyseal ends of both the ulnae and radii, with irregular margins, slightly resembling a flared bell shape. (**G**) Both femurs and tibias show metaphyseal enlargement with irregular margins and slight deformity, and the upper segments of both tibias are slightly inclined; both knees are slightly varus. (**H**) The anteroposterior radiograph of the left wrist indicates that the phalanges are slightly short and thick, with a bullet-shaped appearance.

CUL7 gene mutations and 3M syndrome through experimental validation. Currently, approximately 90 different mutations in this gene have been reported (Table S1).

Research has shown that CUL7 plays a significant role in promoting growth by interacting with p53, reducing its activity, and fostering cell growth.[8] Mutations in CUL7 have the potential to disrupt the Growth Hormone (GH) and Insulin-like Growth Factor I (IGF-I) signaling pathways by accumulating the signaling molecule Insulin Receptor Substrate 1 (IRS-1), leading to growth restriction. In CUL7 knockout cell lines, this accumulation can result in increased activation of IRS-1's downstream Akt and MEK/ERK pathways, and excessive stimulation may, in turn, contribute to cellular senescence.[9]

OBSL1

OBSL1, a member of the UNC-89/Obscurin family, plays a crucial role in the structure of cardiac muscle cells. Geisler et al studied the intracellular protein distribution and domain organization of OBSL1 and proposed that OBSL1 functions as a cytoskeletal adaptor protein.[10] In 2009, Hanson et al identified homozygous or compound heterozygous mutations in the OBSL1 gene in affected individuals from unrelated families with 3M syndrome. By using siRNA to knock down OBSL1, they observed a decrease in CUL7 levels. These findings suggest that both proteins function in the same pathways affecting cell proliferation and human growth.[11] In 2012, Clayton et al revealed functional associations of OBSL1 and CUL7, highlighting their significant roles in the P53-regulated apoptosis pathway. In 2014, Li et al discovered that during the assembly of the 3M complex, OBSL1 can interact with P53, CUL9, and ROC1, provided it is bound to CUL7. Immunoprecipitation experiments in transfected cells further indicated interactions between OBSL1, CCDC8 and CUL7, but no interaction between CCDC8 and CUL7. Therefore, this led to the suggestion that OBSL1 may function as a bridging protein connecting CUL7 and CCDC8.[12] To date, over 30 mutations in this gene have been reported (Table S2).

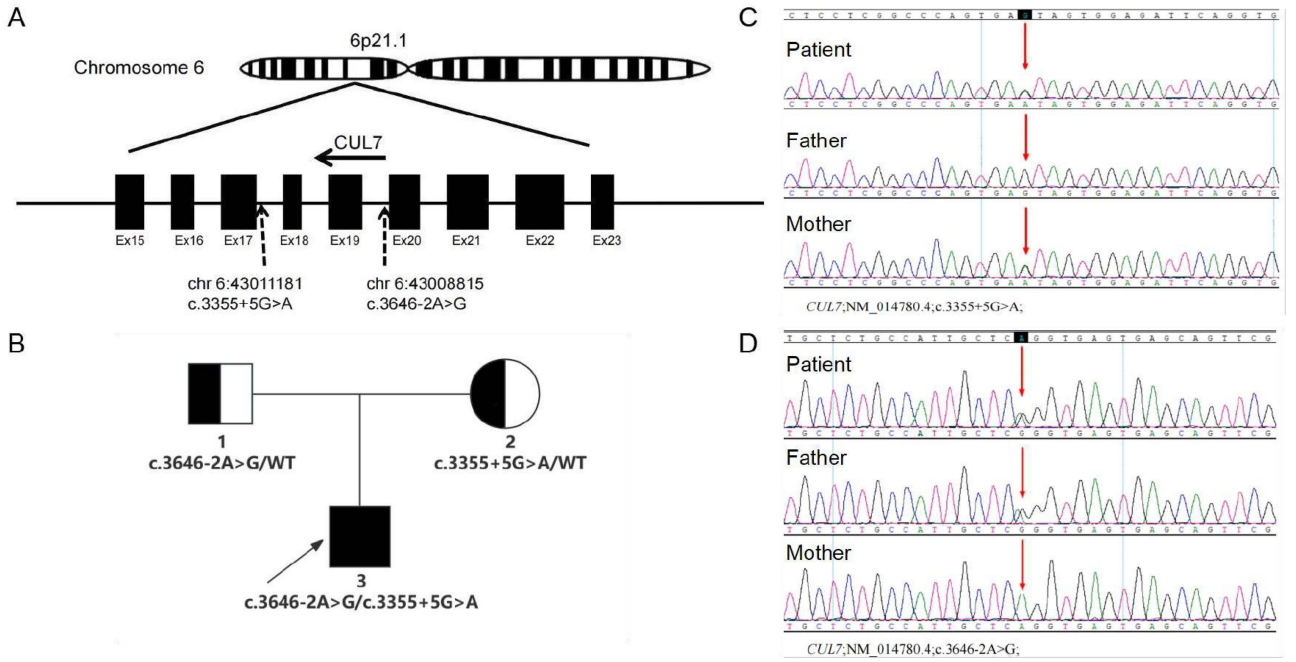

Figure 4 The results of genetic testing. (**A**) The CUL7 gene is located on the short arm of chromosome 6, region 2, band 1. Two mutations are identified in the 17th and 19th intronic regions. (**B–D**) Through Sanger Sequencing, we found that one mutation c.3646–2A>G is inherited from the proband's healthy father, the other mutation c.3355+5G>A is inherited from his healthy mother.

CCDC8

CCDC8 is a gene located on chromosome 19 and contains potential sites for acetylation, glycosylation, phosphorylation, and inositol acylation. In 2011, Hanson et al identified CCDC8 as the third causative gene in 3M syndrome. Two distinct homozygous mutations were found in five affected families. These mutations led to premature stop codons and loss of function.[13] Similar to CUL7, CCDC8 serves as an auxiliary factor in p53-induced apoptosis.[14] Wang et al observed that CCDC8 is primarily localized on the cell membrane of tissues, while CUL7 is present in both the cell membrane and cytoplasm, and OBSL1 is found in both the cell membrane and around the cell nucleus. CCDC8 facilitates the movement of CUL7 and OBSL1 proteins from the cytoplasm to the cell membrane, suggesting that the assembly of the 3M complex possibly occurs on the cell membrane. Further studies revealed that CCDC8 is derived from the Gag protein of

Table 1 The Mutations Information of Proband

Basic Information	Variety Chromosome location Exon/intron	c.3646–2A>G chr6:43008815 In19	c.3355+5G>A chr6:43011181 In17
Population Frequency	Thousand Genomes database Exome Aggregation Consortium (EXAC) Genome Aggregation Database (GnomAD)	NA 0.000009 0.000004	NA 0.000008 0.000008
Mutation Prediction	Combined Annotation Dependent Depletion (CADD) SIFT Mutation Taster SpliceAI	34 NA Damaging Damaging	32 NA NA Damaging
Conservation Prediction	PhyloP Vertebrates PhyloP Placetal Mammals Genomic Evolutionary Rate Profiling (GERP++)	Conversation Conversation Conversation	Conversation Conversation NA

Abbreviation: NA, not available.

a retrotransposon in placental mammals and is phosphorylated by CK2 and GSK3. CCDC8 initially binds to OBSL1, and in combination with CUL7, completes the membrane assembly of the CUL7 E3 ubiquitin ligase complex. Wnt pathway inhibition suppresses CCDC8 phosphorylation and its association with the 3M complex. In a knockout mouse model of the ccdc8 gene, impaired trophoblast migration and placental development were observed, leading to intrauterine growth restriction and perinatal death.[15] Zhang et al generated CCDC8 knockout mice and observed that their body weight and length were significantly lower than those of normal mice.[16] To date, only one additional homozygous mutation in CCDC8 has been reported (Table S3). Consequently, the complete spectrum of gene mutations in CCDC8 remains incompletely elucidated.

Discussion

3M syndrome is a rare autosomal recessive genetic disorder characterized by significant pre- and postnatal growth restriction. The CUL7 gene is located on chromosome 6p21.1 and encodes a large protein consisting of 1698 amino acids, with a relative molecular weight of approximately 192.8 kDa. Arai et al discovered that newborn mice with targeted disruption of the CUL7 gene experienced fatalities due to respiratory distress. In the late stages of pregnancy, the growth retardation of CUL7-deficient embryos became increasingly apparent in comparison to wild-type counterparts. Placentas of CUL7-deficient mice exhibited defects in trophoblast lineage differentiation and abnormal vascular structures.[17] Recent research has shown that defects in the membrane assembly of the E3 ubiquitin ligase complex in mice (composed of CCDC8, OBSL1, and CUL7) can impact trophoblast cell migration and placental development, leading to intrauterine growth restriction and perinatal mortality. In summary, the CUL7 gene is an established causative gene for 3M syndrome.

Our investigation revealed compound heterozygous mutations (c.3646–2A>G and c.3355+5G>A) in the CUL7 gene of the affected infant through whole-exome sequencing. The mutation c.3355+5G>A had been previously identified and reported in a prenatal diagnostic case, resulting in a large base deletions. However, the mutation c.3646–2A>G was a novel finding, demonstrating strong pathogenicity. Computational analysis using SpliceAI—a 32-layer deep residual neural network that predicts RNA splicing patterns directly from genomic sequence data without relying on predefined splice-site motifs (eg, GT-AG dinucleotides)—strongly supported the pathogenicity of these splice-site variants. The algorithm quantifies splice-site disruption by calculating Δscores (Δscore/DS), representing the change in predicted splice probability (donor, acceptor, or non-splice site) between reference and variant sequences: c.3646–2A>G: Converts the canonical AG acceptor dinucleotide to GG, with a high acceptor loss score (DS_AL = 0.94, DP_AL = −2). This disrupts intron termination, resulting in exon skipping; c.3355+5G>A: Alters the conserved GT donor dinucleotide to AT, with a near-maximal donor loss score (DS_DL = 0.99, DP_DL = 5). This impairs intron excision, leading to intron retention.[18,19] The absence of mutations in the other two major 3M syndrome-associated genes (OBSL1 and CCDC8) significantly strengthens the genotype-phenotype correlation and reinforces CUL7's role in driving the observed clinical manifestations. Furthermore, this compound heterozygote of CUL7 gene is the first case with two variant splice mutations.

Antenatal anomalies were exclusively detected through ultrasound examination. A definitive prenatal diagnosis could not be established as his guardian declined invasive genomic testing due to personal considerations. Postnatal confirmation was achieved through clinical phenotyping, skeletal radiography, and trio exome sequencing. Intrauterine growth restriction is a non-specific finding occurring in approximately 0.17% of all live births.[19] In reported prenatal diagnostic cases, affected individuals displayed different phenotypes, including increased NT, long bone hypoplasia, hypoplastic thorax, and distinctive facial features.[20] Additionally, distinguishing 3M syndrome from other fetal intrauterine growth retardation syndromes poses a significant challenge. Therefore, combining clinical presentation with genomic sequencing is crucial for accurate prenatal diagnosis.

Highlights

1. A novel pathogenic variant in CUL7 was identified.
2. The clinical features strongly matched the genetic disorder's expected presentation.
3. This study summarizes known genetic variants associated with 3M syndrome.

Abbreviations

CUL7, Cullin 7; OBSL1, Obscurin-Like 1; CCDC8, Coiled-coil domain containing 8; NT, nuchal translucency; WES, Whole-exome sequencing; SNVs, single-nucleotide variants; SD, standard deviation; ESP, Exome Sequencing Project; EXAC, the Exome Aggregation Consortium; GnomAD, Genome Aggregation Database; GH, Growth Hormone; IGF-I, Insulin-like Growth Factor I; IRS-1, Insulin Receptor Substrate 1.

Data Sharing Statement

The original data presented in the study are included in this article. Further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

The study protocol has gained approval from the Ethics Committee of Yuying Children's Hospital of Wenzhou Medical University (2023-K-148-01). Given the minor patient's young age, written informed consent for participation in the study was obtained from the patient's legal guardians.

Acknowledgment

We thank all the participants in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Feldmann M, Gilgenkrantz S, Parisot S, Zarini G, Marchal C. 3M dwarfism: a study of two further sibs. *J Med Genet*. 1989;26(9):583–585. doi:10.1136/jmg.26.9.583
2. Huber C, Munnich A, Cormier-Daire V. The 3M syndrome. *Best Pract Res Clin Endocrinol Metab*. 2011;25(1):143–151. doi:10.1016/j.beem.2010.08.015
3. Miller JD, McKusick VA, Malvaux P, Temtamy S, Salinas C. The 3-M syndrome: a heritable low birthweight dwarfism. *Birth Defects Original Article Series*. 1975;11(5):39–47.
4. Huang Y, Mei L, Zhang J, Chen X, Wang W, Ge Y. [Clinical and molecular genetic analysis of a patient with 3-M syndrome]. *Zhonghua yi xue yi chuan xue za zhi*. 2021;38(12):1237–1240. doi:10.3760/cma.j.cn511374-20200929-00702
5. Huber C, Dias-Santagata D, Glaser A, et al. Identification of mutations in CUL7 in 3-M syndrome. *Nat Genet*. 2005;37(10):1119–1124. doi:10.1038/ng1628
6. Huber C, Delezoide AL, Guimiot F, et al. A large-scale mutation search reveals genetic heterogeneity in 3M syndrome. *Eur J Hum Genet*. 2009;17(3):395–400. doi:10.1038/ejhg.2008.200
7. Majewski F, Goecke T. Studies of microcephalic primordial dwarfism I: approach to a delineation of the Seckel syndrome. *Am J Med Genet*. 1982;12(1):7–21. doi:10.1002/ajmg.1320120103
8. Andrews P, He YJ, Xiong Y. Cytoplasmic localized ubiquitin ligase cullin 7 binds to p53 and promotes cell growth by antagonizing p53 function. *Oncogene*. 2006;25(33):4534–4548. doi:10.1038/sj.onc.1209490
9. Xu X, Sarikas A, Dias-Santagata DC, et al. The CUL7 E3 ubiquitin ligase targets insulin receptor substrate 1 for ubiquitin-dependent degradation. *Mol Cell*. 2008;30(4):403–414. doi:10.1016/j.molcel.2008.03.009
10. Geisler SB, Robinson D, Hauringa M, et al. Obscurin-like 1, OBSL1, is a novel cytoskeletal protein related to obscurin. *Genomics*. 2007;89(4):521–531. doi:10.1016/j.ygeno.2006.12.004
11. Hanson D, Murray PG, Sud A, et al. The primordial growth disorder 3-M syndrome connects ubiquitination to the cytoskeletal adaptor OBSL1. *Am J Hum Genet*. 2009;84(6):801–806. doi:10.1016/j.ajhg.2009.04.021

12. Li Z, Pei XH, Yan J, et al. CUL9 mediates the functions of the 3M complex and ubiquitylates survivin to maintain genome integrity. *Mol Cell*. 2014;54(5):805–819. doi:10.1016/j.molcel.2014.03.046
13. Hanson D, Murray PG, O'Sullivan J, et al. Exome sequencing identifies CCDC8 mutations in 3-M syndrome, suggesting that CCDC8 contributes in a pathway with CUL7 and OBSL1 to control human growth. *Am J Hum Genet*. 2011;89(1):148–153. doi:10.1016/j.ajhg.2011.05.028
14. Dai C, Tang Y, Jung SY, Qin J, Aaronson SA, Gu W. Differential effects on p53-mediated cell cycle arrest vs. apoptosis by p90. *Proc Natl Acad Sci U S A*. 2011;108(47):18937–18942. doi:10.1073/pnas.1110988108
15. Wang P, Yan F, Li Z, Yu Y, Parnell SE, Xiong Y. Impaired plasma membrane localization of ubiquitin ligase complex underlies 3-M syndrome development. *J Clin Invest*. 2019;129(10):4393–4407. doi:10.1172/JCI129107
16. Zhang L, Ren D, Hu X, et al. Establishment of the 3M syndrome animal model in CCDC8 knockout mice. *Mol Biomed*. 2023;4(1):24. doi:10.1186/s43556-023-00136-0
17. Arai T, Kasper JS, Skaar JR, Ali SH, Takahashi C, DeCaprio JA. Targeted disruption of p185/Cul7 gene results in abnormal vascular morphogenesis. *Proc Natl Acad Sci U S A*. 2003;100(17):9855–9860. doi:10.1073/pnas.1733908100
18. Breathnach R, Chambon P. Organization and expression of eucaryotic split genes coding for proteins. *Annu Rev Biochem*. 1981;50:349–383. doi:10.1146/annurev.bi.50.070181.002025
19. Breckenridge DG, Watanabe Y, Greenwood SJ, Gray MW, Schnare MN. U1 small nuclear RNA and spliceosomal introns in Euglena gracilis. *Proc Natl Acad Sci U S A*. 1999;96(3):852–856. doi:10.1073/pnas.96.3.852
20. Hu X, Li H, Gui B, et al. Prenatal and early diagnosis of Chinese 3-M syndrome patients with novel pathogenic variants. *Clin Chim Acta*. 2017;474:159–164. doi:10.1016/j.cca.2017.09.022