



3M syndrome patient with a novel mutation: A case report

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Abstract

BACKGROUND

A rare autosomal recessive genetic disorder, 3M syndrome, is characterized by severe intrauterine and postnatal growth retardation. Children with 3M syndrome typically exhibit short stature, facial deformities, long tubular bones, and high vertebral bodies but generally lack mental abnormalities or other organ damage. Pathogenic genes associated with 3M syndrome include *CUL7*, *OBSL1* and *CCDC8*. The clinical and molecular characteristics of patient with 3M syndrome are unique and serve as important diagnostic indicators.

CASE SUMMARY

In this case, the patient displayed square shoulders, scoliosis, long slender tubular bones, and normal neurological development. Notably, the patient did not exhibit the typical dysmorphic facial features, relative macrocephaly, or growth retardation commonly observed in individuals with 3M syndrome. Whole exon sequencing revealed a novel heterozygous c.56681+1G>C (Splice-3) variant and a previously reported nonsense heterozygous c.3341G>A (p.Trp1114Ter) variant of *OBSL1*. Therefore, it is important to note that the clinical features of 3M syndrome may not always be observable, and genetic confirmation is often required. Additionally, the identification of the c.5683+1G>C variant in *OBSL1* is noteworthy because it has not been previously reported in public databases.

CONCLUSION

Our study identified a new variant (c.5683+1G>C) of *OBSL1* that contributes to expanding the molecular profile of 3M syndrome.

Key Words: 3M syndrome; *CUL7*; *OBSL1*; *CCDC8*; Autosomal recessive; Case report

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Core Tip: 3M syndrome, a rare autosomal recessive genetic disease that is characterized by severe intrauterine and postnatal growth retardation. Children with 3M syndrome typically exhibit short stature, facial deformities, long tubular bones, and high vertebral bodies, while lacking mental abnormalities or other organ damage. The pathogenic genes associated with 3M syndrome include *CUL7*, *OBSL1* and *CCDC8*. When encountering patients with short stature and dysmorphic features alongside normal intelligence, it is essential to consider 3M syndrome as a differential diagnosis. Our study has identified a new variant in the *OBSL1* gene, contributing to the expanding molecular profile of 3M syndrome.

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INTRODUCTION

3M syndrome (OMIM#273750), a rare autosomal recessive disease, was first discovered in 1975 by Miller *et al*[1]. Since then, approximately 200 cases have been reported worldwide, including eight in China.

Notably, the prevalence of 3M syndrome may be underestimated due to the possibility of normal mental development; therefore, the actual number of cases could be higher than that previously reported[2].

Typically, 3M syndrome is associated with distinctive facial deformities such as a triangular face, protruding forehead, flat nose, upturned nostrils, full lips, and a wide jaw. However, in the present case, the facial features appeared normal. Additionally, skeletal abnormalities, including hyperlordosis, slender long bones, prominent fleshy heels, joint hypermobility, and congenital hip dislocation, are often observed in individuals with 3M syndrome[3]. Other physical characteristics that may be present include a short neck, square shoulders, sternal abnormalities, narrow thorax, winged scapulae, lordosis, joint laxity, brachydactyly of the fifth finger, and rocker-bottom feet[3]. It is important to note that the intellectual and endocrine functions were unaffected[4].

Diagnosis of 3M syndrome is primarily based on clinical and radiological findings, which are further confirmed through genetic analysis. Three pathogenic genes associated with 3MS have been identified: *CUL7* on chromosome 6p21.1, *OBSL1* on chromosome 2q35-36.1, and *CCDC8* on chromosome 19q13.2-q13.32[5-7]. Because of the different mutated genes, 3M syndrome is categorized into three distinct types: type 1, type 2 and type 3, with incidence rates of 77.5%, 16.3% and 6%, respectively[8].

CUL7 is responsible for encoding the cullin 7 (*CUL7*) protein, which serves as a scaffold protein and is a vital component of an E3 ubiquitin ligase enzyme. Nonsense or missense mutations in the *CUL7* gene prevent the substrate from ubiquitinating, degrading, and accumulating in the body. *OBSL1* encodes a cytoskeletal adaptor protein that is primarily localized within the prenuclear region. The exact function of obscurin-like 1 (*OBSL1*) is still under investigation; however, recent studies have highlighted its interaction with the protein encoded by *CCDC8*. This interaction is essential for p54-mediated apoptosis in cells. The function of coiled-coil domain-containing protein 8 (*CCDC8*) remains largely unknown. Unraveling the precise mechanisms governing this intricate relationship is crucial for understanding the physiological and pathological implications associated with these proteins[9].

In this report, we present a comprehensive assessment of the clinical and molecular manifestations in a 3M syndrome patient. We performed whole-exon sequencing to confirm the diagnosis and identified a novel variant of *OBSL1*, thereby expanding our understanding of the molecular spectrum of this syndrome in the Chinese population.

CASE PRESENTATION

Chief complaints

A 15-year-old woman was referred to the orthopedic clinic for a lateral curvature.

History of present illness

The patient was found to have high and low shoulders, spinal deformity, and low back pain after walking 2 years ago. Notably, the patient did not have any relevant past interventions with outcomes for the final diagnosis.

History of past illness

The patient was generally in good health. No medical history or close contact history of diabetes, hypertension, coronary heart disease, hepatitis, tuberculosis or other infectious diseases, no surgical history, no trauma history, no blood product infusion history, no food or drug allergy history, vaccination history as planned.

Personal and family history

Sequencing analysis revealed that the patient's parents were heterozygous carriers, with the father carrying the c.5683+1G>C variant and the mother carrying the c.3341G>A variant (Figure 1).

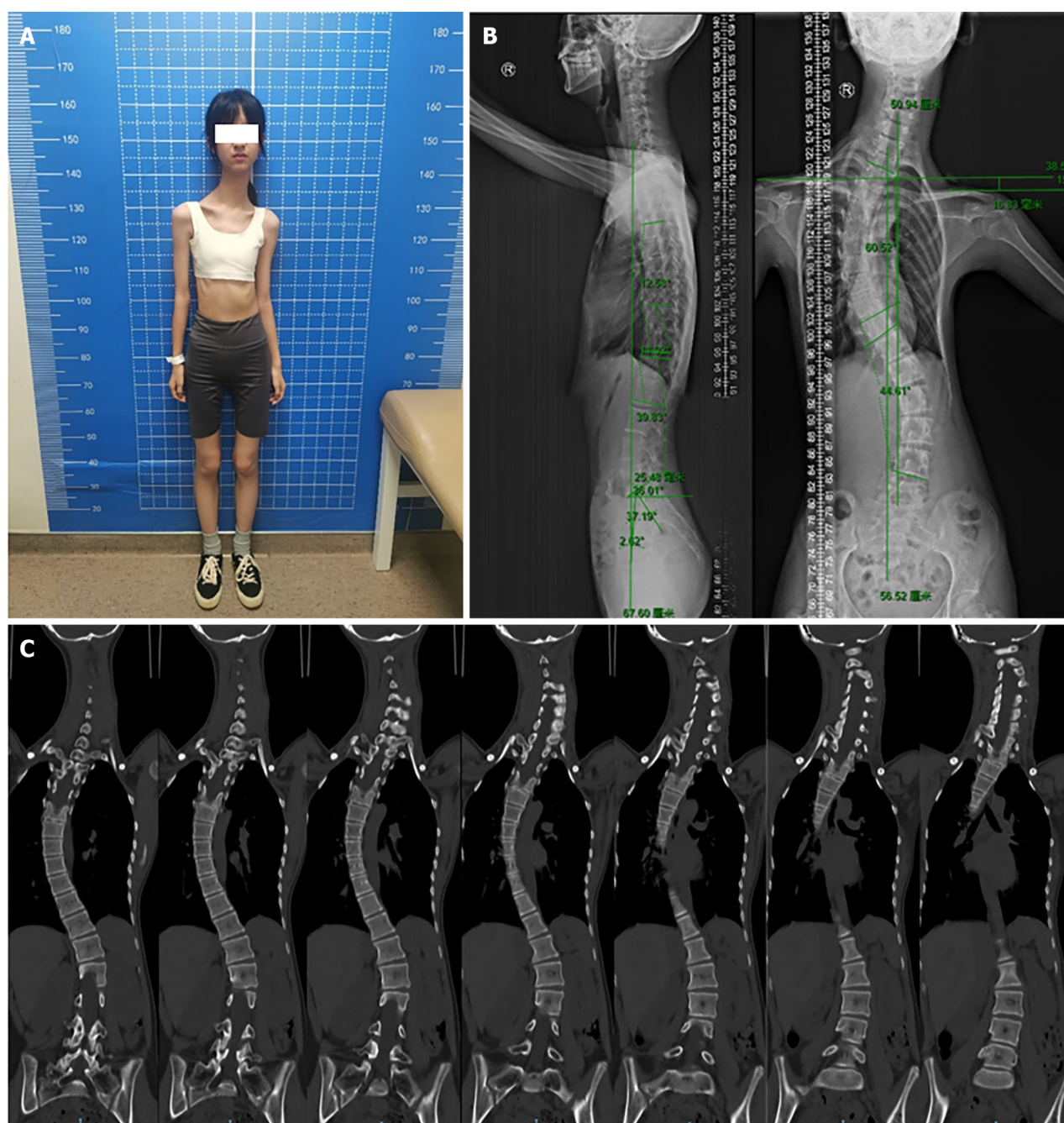


Figure 1 Clinical features of 3M syndrome. A: Facial and body features; B: X-rays showing the slender long tubular bones, thoracic scoliosis, tall vertebral bodies and small pelvis; C: Computed tomography showing the thoracic scoliosis and tall vertebral bodies.

Physical examination

She was 166 cm tall and weighed only 30 kg, with a body mass index of 10.89. Further examination revealed several dysmorphic features, including square shoulders, slender tubular bones, scoliosis, and a small pelvis (Figure 2). The endocrine function and intelligence of the patient were normal (Table 1). The patient presented with tachycardia, anterior mitral valve prolapse, and mild tricuspid valve insufficiency.

Laboratory examinations

Lung function tests indicated restrictive ventilation dysfunction, with maximum voluntary ventilation of > 70%. EDTA-anticoagulated blood samples were collected from the patients after obtaining informed consent from their guardians. Genomic DNA was extracted from whole blood using standard procedures. In this study, we used whole-exon sequencing to sequence *CUL7* (NM_001168370), *OBSL1* (NM_015311) and *CCDC8* (NM_032040) genes[10]. In this case, the heterozygous variants in *OBSL1* (NM_015311) were c.5683+1G>C (Splice-3) and c.3341G>A (p.Trp1114Ter). *OBSL1* consists of a protein with 4 tandem N-terminal immunoglobulin (Ig)-like domains, a central fibronectin domain, and 13 C-terminal Ig domains. The nonsense mutation c.3341G>A (p.Trp1114Ter) is located in exon10, the IGc2 domain of the protein (amino acid positions 1095–1160). The mutation prematurely terminates the translation of the protein and

Table 1 Clinical characteristics and molecular findings of the patient

Age	15 yr
Gender	Female
Weight	30 kg
Height	166 cm
BMI	10.89
Facial features	
Relative macrocephaly	-
Dolichocephaly	-
Triangular face	-
Hypoplastic midface	-
Fleshy nasal tip	-
Long philtrum	-
Full lips	-
Pointed chin	-
Musculoskeletal features	
Short broad neck	-
Square shoulders	+
Short thorax	-
Sternal anomaly	-
Hyperlordosis	-
Generalized or isolated joint hypermobility	-
Prominent heels, and pes planus	-
Genitourinary anomalies	-
Intelligence	Normal
Radiographic features	
Long slender tubular bones	+
Tall vertebra	-
Wedging of the thoracic vertebral bodies	-
Thoracic kyphoscoliosis	+
Small pelvis	+
Molecular findings	
Karyotype	46, XX
Gene	OBSL1(NM_015311)
Variation (DNA)	c.5683+1G>C and c.3341G>A
Variation (protein)	Splice-3 and p.Trp1114Ter
Novelty	Novel and Known
ACMG classification	Pathogenic

ACMG: The American College of Medical Genetics and Genomics; BMI: Body mass index.

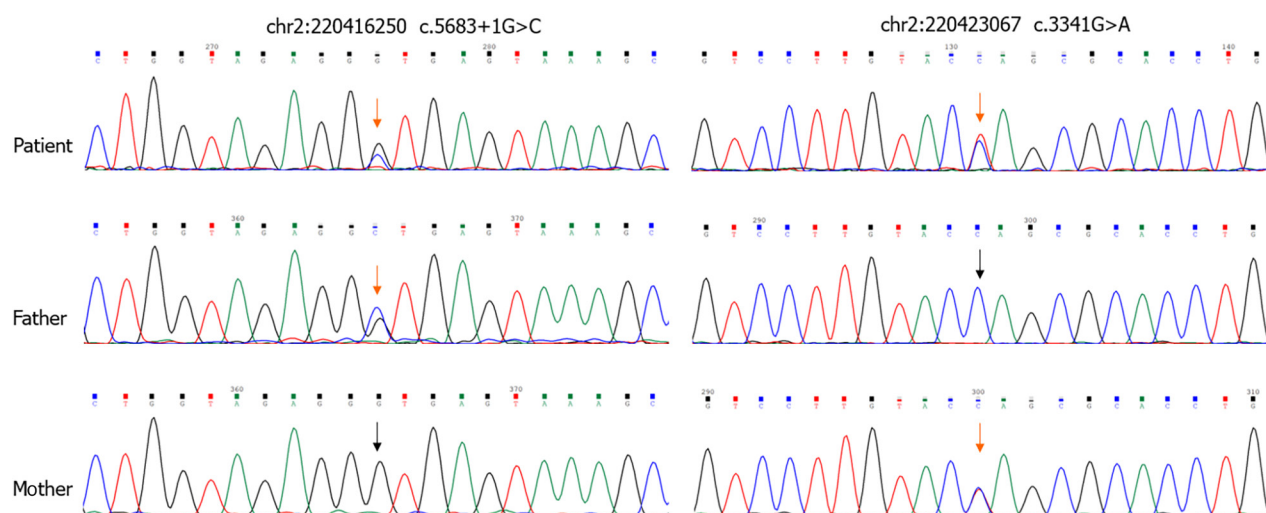


Figure 2 Schematic representation of protein and compound heterozygous variants in *OBSL1*. Sequence analysis of *OBSL1* showing heterozygous variant c.5683+1G>C (Splice-3) in intron and c.3341G>A (p.Trp1114Ter) in exon derived from the father and mother, respectively. Father were heterozygous for the c.5683+1G>C variant and mother were heterozygous for the c.3341G>A variant.

prevents subsequent amino acid synthesis, which includes several domains. The IG domain may be involved in a variety of functions in proteins, such as intercellular recognition, cell surface receptors, muscle structure, and the immune system, so the mutation may affect the normal physiological function of the protein. The c.5683+1G>C mutation is located on the intron, which is located at the classical splicing site and is predicted by the software to potentially affects mRNA splicing, which leads to decreased *OBSL1* protein expression and loss of protein function, contributing to disease occurrence. Notably, the c.5683+1G>C variant has not been previously reported. Sequencing analysis revealed that the patient's parents were heterozygous carriers, with the father carrying the c.5683+1G>C variant and the mother carrying the c.3341G>A variant (Figure 1).

Imaging examinations

X-rays showing the slender long tubular bones, thoracic scoliosis, tall vertebral bodies and small pelvis (Figure 2B). Computed tomography (CT) showed thoracic scoliosis and tall vertebral bodies (Figure 2C).

FINAL DIAGNOSIS

3M syndrome with scoliosis.

TREATMENT

Spinal orthopedic surgery.

OUTCOME AND FOLLOW-UP

The patient was still alive.

DISCUSSION

The case from a Chinese family with imaging characteristics and dysmorphological findings were partially consistent with those of 3M syndrome. The patient was evaluated by a proficient clinical orthopedist. Demographic information, family medical history, clinical manifestations, and radiological findings were extracted from hospital records.

Clinical records were retrospectively reviewed to extract the epidemiological data (sex, age, consanguinity, geographical origin, and personal history); clinical features (facial dysmorphisms, psychomotor and intellectual development, thoracic deformities, spinal anomalies, and limb abnormalities); and radiological findings (radiography and CT)[2]. All patient-specific information was properly deidentified to ensure privacy.

3M syndrome is a rare autosomal recessive disease. This syndrome causes severe intrauterine and postnatal growth retardation, facial deformities and skeletal malformations; however, intelligence and endocrine function remain unaffected. Its diagnosis is primarily based on gene sequencing; however, the prognosis remains unclear.

In previous studies, the disease locus gene was mapped to chromosome 6p21.1 using a homozygosity mapping strategy, leading to the identification of mutations in the *CUL7* gene. *CUL7* (6p21.1) is the major gene associated with 3M syndrome, accounting for 77.5% of cases[5]. Other mutations involve *OBSL1* (2q35) in 16.3% of cases and *CCDC8* (19q13.33) in 6% of cases[11].

CUL7, *OBSL1* and *CCDC8* physically interact with each other to form the 3M complex, which plays a crucial role in maintaining microtubule and genome integrity[12]. Disruption of this complex results in microtubule damage, abnormal chromosomal separation and cell death. However, the exact mechanism underlying 3M syndrome development remains unclear. It is evident that there is still much to be discovered about the intricate functions and interactions of *CUL7*, *OBSL1* and *CCDC8*. Moreover, the detailed mechanisms responsible for the growth impairments observed in the 3M syndrome remain largely unclear.

According to the human gene mutation database (<http://www.hgmd.cf.ac.uk>), 88 published variants of *CUL7* and 36 of *OBSL1* lead to 3M syndrome. The most common variants include frameshift, nonsense and missense mutations. In this case, one variant was a nonsense mutation, whereas the other was affected by splicing. It is rare to have two mutations simultaneously, which may also lead to more severe developmental abnormalities; however, the patient's intellectual development remains unaffected. Similarly, determining whether a direct relationship exists between scoliosis and genetic mutations in patients requires additional case data.

It is noteworthy that *CUL7*, *OBSL1* and *CCDC8* are responsible for 98% of 3MS cases without a consistent genotype-phenotype correlation[8]. For orthopedists, it is important to provide symptomatic treatment and follow-up care, considering the high likelihood of encountering patients with this syndrome. In this case, growth hormone (GH) therapy remains controversial owing to individual differences and the treatment effectiveness[11]. Although the patient had normal GH levels, GH therapy should be considered to address the severe short stature commonly associated with 3M syndrome despite the absence of growth restriction in this patient. The duration of treatment should be determined based on the height gain and growth rate.

While the prenatal diagnosis of 3M syndrome is a topic of debate due to normal intelligence, preimplantation genetic diagnosis is of great importance for families aiming to have a healthy child.

In conclusion, when encountering patients with short stature and dysmorphic features along with normal intelligence, it is essential to consider 3M syndrome as a differential diagnosis. Genetic sequencing of *CUL7*, *OBSL1* and *CCDC8* is necessary to confirm the clinical diagnosis and provide appropriate genetic counseling.

CONCLUSION

Our study identified a new variant (c.5683+1G>C) of *OBSL1* that contributes to expanding the molecular profile of 3M syndrome.

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FOOTNOTES

Co-first authors: Ming-Ran Luo and Si-Ming Dai.

Co-corresponding authors: Shu-Jie Zhao and Guo-Yong Yin.

Author contributions: Luo MR and Dai SM contributed equally to this work as joint first authors; Zhao SJ and Yin GY contributed equally to this work as joint corresponding authors; Luo MR and Dai SM were involved in drafting and revision of the manuscript; Zhao SJ and Yin GY were involved in completing the collection and sequencing of clinical samples; Yin GY supervised this study. All authors discussed the results and commented on the manuscript. All authors performed the data analysis, and statistical analysis. The reasons for designating Zhao SJ and Yin GY as joint corresponding authors are threefold. First, Zhao SJ and Yin GY conceived, designed and refined the study protocol. The research was performed as a collaborative effort, and the designation of joint corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of joint corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Zhao SJ and Yin GY contributed efforts of equal substance throughout the research process. The choice of these researchers as joint corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Zhao SJ and Yin GY as joint corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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