89801_Auto_Edited.docx

WORD COUNT 1771
TIME SUBMITTED 18-JAN-2024 04:09PM
PAPER ID 106237968

Name of Journal: *World Journal of Clinical Cases*
Manuscript NO: 89801
Manuscript Type: CASE REPORT

A 3M Syndrome Patient with a Novel Mutation: A case report from China

Mingran Luo, Siming Dai, Yin Li, Qian Wang, Hao Liu, Peng Gao, Jiayun Liu, Jian Chen, Shujie Zhao, Guoyong Yin

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 (Cullin7), OBSL1 (Obscurin-Like1), and CCDC8 (Coiled-coil domain containing 8, also P90). 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 3MS.

INTRODUCTION

The 3M syndrome (3MS) (OMIM#273750), a rare autosomal recessive disease, was first discovered in 1975 by Miller, McKusick, and Malvaux [1]. Since then, approximately 200 cases have been reported worldwide, including 8 cases in China.

Notably, the prevalence of 3MS 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, 3MS 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 3MS [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 3MS 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 (cullin 7) on chromosome 6p21.1, OBSL1 (obscurin-like 1) on chromosome 2q35-36.1, and CCDC8 (coiled-coil domain-containing protein 8) on chromosome 19q13.2-q13.32 [5-7]. Because of the different mutated genes, 3MS 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 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, this particular protein encodes a cytoskeletal adaptor protein that is primarily localized within the prenuclear region. The exact function of 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 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 3MS 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 girl 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 2).

Physical examination

She was 166 cm tall and weighed only 30 kg, with a BMI (body mass index) of 10.89. Further examination revealed several dysmorphic features, including square shoulders, slender tubular bones, scoliosis, and a small pelvis (Figure 1). 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 (MVV) 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 to 1160). The mutation prematurely terminates

the translation of the protein and 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 2).

Imaging examinations

X-rays showing the slender long tubular bones, thoracic scoliosis, tall vertebral bodies and small pelvis (Figure 1B). CT showing the thoracic scoliosis and tall vertebral bodies (Figure 1C).

MULTIDISCIPLINARY EXPERT CONSULTATION

none

FINAL DIAGNOSIS

3M syndrome with scoliosis

TREATMENT

Spinal orthopaedic surgery

OUTCOME AND FOLLOW-UP

The patient was still alive.

DISCUSSION

The cases from a Chinese family with imaging characteristics and dysmorphological findings were partially consistent with those of 3MS. 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.

The 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 is the major gene associated with 3M syndrome, accounting for 77.5% of cases [5]. Other mutations involve OBSL1 (2q35) in 28% of cases and CCDC8 (19q13.33) in 5% 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 3MS 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 3MS. The most common variants include frameshift, nonsense, and missense mutations [13]. 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 3MS 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 3MS 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 3MS 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 3MS.

ACKNOWLEDGEMENTS

We would like to thank the 3MS patient and her family for supporting this work.

89801_Auto_Edited.docx

ORIGINALITY REPORT

10%
SIMILARITY INDEX

PRIMARY SOURCES

1	Esra Isik, Duygu Arican, Tahir Atik, Joo Enn Ooi et al. " A rare cause of syndromic short stature: syndrome in three families ", American Journal of Medical Genetics Part A, 2020 Crossref	56 words — 3%
2	Khaoula Khachnaoui-Zaafrane, Ines Ouertani, Amira Zanati, Hajer Kandara, Faouzi Maazoul, Ridha Mrad. "3M syndrome: A Tunisian seven-cases series", European Journal of Medical Genetics, 2022 Crossref	46 words — 2%
3	www.ncbi.nlm.nih.gov Internet	22 words — 1%
4	Liangjie Guo, Zhanqi Feng, Xiaoye Jin, Shanshan Yin, Mengting Zhang, Yue Gao, Bo Zhang, Hongdan Wang, Lin Liu. "A novel mutation within intron 17 of the CUL7 gene results in appearance of premature termination codon", Clinica Chimica Acta, 2020 Crossref	18 words — 1%
5	Albert Youngwoo Jang, Pyung Chun Oh, Jin Mo Kang, Chul Hyun Park, Woong Chol Kang. "Extensive complex thoracoabdominal aortic aneurysm salvaged by surgical graft providing landing zone for endovascular graft: A case report", World Journal of Clinical Cases, 2022 Crossref	13 words — 1%

6	www.cusabio.com Internet	12 words — 1%
7	www.mdpi.com Internet	12 words — 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS