

Familial 3M Syndrome – as an Example of Diagnostic Difficulties in Rare Genetic Syndromes

Magdalena Pasińska¹, Joanna M Rusecka², Agnieszka Sobczyńska-Tomaszewska², Maciej Pasiński³

¹Faculty of Medicine, Department of Clinical Genetics, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Bydgoszcz, Poland; ²Medical Center Medgen, Warsaw, Poland; ³Department of Orthopedics and Traumatology of the Locomotor System, Antoni Jurasz University Hospital No. 1, Bydgoszcz, Poland

Correspondence: Magdalena Pasińska, Department of Clinical Genetics, Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Skłodowskiej - Curie 9, Bydgoszcz, 85-094, Poland, Tel/Fax +52 585 35 68, Email magdapas@wp.pl; magdalena@cm.umk.pl

Introduction: A lack of experience diagnosing and treating rare diseases contributes to delayed or incorrect diagnoses, and optimal clinical treatment is often unachievable. Miller-McKusick-Malvaux syndrome (3M syndrome, also known as dolichospondylic dysplasia) is a rare genetic disorder with unknown prevalence. It is inherited in an autosomal recessive manner and is characterized by severe intrauterine and postnatal growth retardation, dysmorphic facial features, and skeletal abnormalities.

Methods: Whole exome sequencing (WES) was performed on the proband using Twist Human Core Exome Plus Kit (Twist Bioscience) and sequenced with Illumina technology (100x depth of mean coverage). Alignment and variant calling were performed with an in-house bioinformatics pipeline. The identified variants were annotated using the Ensembl VEP and multiple databases, including ClinVar, dbSNP, HGMD, and GnomAD. XHMMv1.0.

Results: This article presents the diagnostic process in siblings diagnosed with 3M syndrome, caused by homozygous variant c.3523C > T (p.His1175Tyr) in the *CUL7* gene.

Discussion: This is the first description of a familial syndrome from a local population. Identifying new gene variants has helped expand the spectrum of variations associated with the pathogenesis of 3M syndrome. The expanding database of genetic variants, combined with knowledge of the spectrum and severity of a patient's clinical symptoms, provides the opportunity to identify genotype-phenotype correlation relevant to medical care.

Keywords: 3M syndrome, skeletal dysplasia, rare diseases, *CUL7* gene, short stature

Introduction

Rare diseases occur in almost 10% of the population and are a major clinical challenge. The diagnostic odyssey often experienced by patients with rare diseases reflects the complexity and length of the journey toward an accurate diagnosis, frequently involving multiple specialists, misdiagnoses, and years of uncertainty. Moreover, optimal clinical treatment is often unachievable.¹ Despite often distinctive clinical features, diagnosing skeletal dysplasias remains challenging due to the complex genotype-phenotype correlations. The significant genetic heterogeneity, overlapping phenotypic presentations among different disorders, and variable expressivity within the same condition complicate the diagnostic process and often require comprehensive genetic analysis to achieve an accurate diagnosis.

Miller-McKusick-Malvaux syndrome (3M syndrome) (MIM #273750) is a rare genetic disorder with unknown prevalence. It is an autosomal recessive disease characterized by severe intrauterine and postnatal growth retardation, dysmorphic facial features, and skeletal abnormalities.^{2,3} To this date, approximately 300 cases have been reported worldwide.³ However, the prevalence of 3M syndrome is most likely underestimated due to the presence of typical, similar clinical features, both prenatally and postnatally, in children with growth retardation and usually with normal mental development and discrete facial dysmorphia.³⁻⁵ Clinical diagnosis is also made more difficult because skeletal changes in the spine, especially in the lumbar region, such as high vertebral bodies and reduced anteroposterior and transverse diameter, become more prominent with age. Previously, the diagnosis of 3M syndrome was made mainly

based on clinical symptoms and radiographic findings, which, although abnormal, are not diagnostic as similar radiographic changes are also found in other growth disorders.^{5,6}

The pace of development and increasing availability of molecular techniques offer the opportunity to link a patient's phenotypic characteristics to the genetic basis of the disease. Advances in genetic technologies have led to the identification of variants in the *CUL7*, *OBSL1*, and *CCDC8* genes, which are responsible for 3M syndrome.^{2,3} Identifying pathogenic variants, in conjunction with the clinical presentation, can lead to earlier diagnosis, indicating new treatment plans and/or interventions, and providing families with information about the risk of the disease in the family and options to avoid it in carriers of pathogenic alterations.^{1,7,8}

In this article, we present the diagnostic process in siblings diagnosed with 3M syndrome, conditioned by the presence of the c.3523C > T (p.His1175Tyr) variants in both alleles of the *CUL7* gene (NM_014780.5). This is the first description of a familial case of the 3M syndrome in a local population, contributing to the existing literature on rare diseases, such as the 3M syndrome.

Material

Siblings of case IV:1 and IV:3 and related parents: III:4 and III:5. [Figure 1](#).

Case (IV:1)

The patient was born from a first pregnancy at 42 weeks of gestation, with a birth weight of 2750 g, a length of 50 cm, and a score of 9 points on the Apgar scale. The head circumference was 34 cm, and the chest circumference was 25 cm. The mother's pregnancy was complicated by toxoplasmosis, treated from the 18th week of pregnancy with Rovamycin. Postnatal physical examination revealed dysmorphic features, including a triangular face, low nasal bridge, prominent forehead, epicanthal folds, downward-slanting palpebral fissures, bilateral transverse palmar creases, shortening of the proximal long bones of both upper and lower limbs, a narrow thorax, and a prominent abdomen. Additionally, generalized joint hypermobility was observed. Based on the clinical presentation and radiological findings, a clinical diagnosis of 3M syndrome was established at the age of 6 years. From the age of 8 to 16, the patient was treated with recombinant human insulin-like growth factor 1 (rhIGF-1).

The boy began to sit at 8 months of age and started walking at 15 months. He exhibited learning difficulties and completed vocational school. At the age of 18, his height was 155 cm. Clinical examination revealed a sunken chest

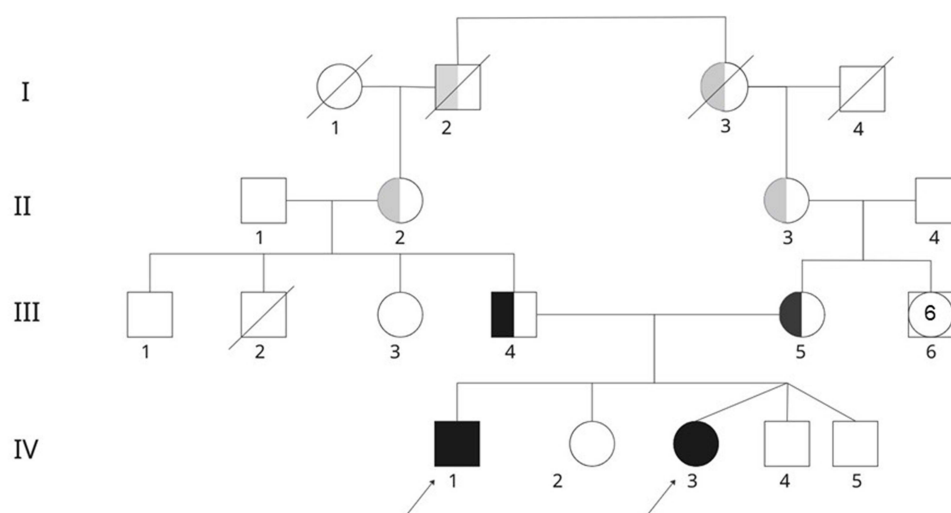


Figure 1 Family pedigree. Affected homozygous individuals are depicted with a fully filled symbol, while individuals carrying the variant in a heterozygous state without clinical symptoms are represented by a split symbol.

Notes: White symbol (square or circle) – healthy individual. Black symbol (square or circle) – individual with 3M syndrome. Half-black, half-white symbol (square or circle) – carrier of the *CUL7* gene variant. Half-gray, half-white (square or circle) – obligatory carrier (not tested). Oblique line through a symbol – deceased individual. Arrow – proband.

(pectus excavatum), thoracolumbar scoliosis, and marked hyperkeratosis on the dorsum of the hands. His hands are frequently very cold. Additionally, he experiences recurrent knee dislocations.

Orthopedic examination and radiographic imaging at the age of 18 revealed short stature and a scoliosis-compensated body habitus with a broad and stocky build, a short thorax with a funnel-shaped sternum, and flattened anteroposterior chest dimension, and loss of normal spinal curvatures. Additionally, features of dolichocephaly with reduced interorbital distance (hypotelorism) were noted, while overall head proportions remained normal. The patient also exhibited a short neck with prominent trapezius muscles. Limb proportions were preserved with slightly increased foot size. Gait and gross motor function were assessed as symmetrical, with no significant deviations from physiological norms. [Figure 2](#).

Radiographic findings demonstrated thoracolumbar scoliosis with vertebral torsion and wedging in the thoracic spine, increased vertebral body height in the lumbar region, and reduced anteroposterior diameter of vertebral bodies. Ribs appeared slender and horizontally oriented on chest X-ray. [Figures 3 and 4](#). Additionally, the pelvis was narrow with decreased size of the pubic bones. [Figure 5](#).

Case (IV:3)

The child was born from the third pregnancy, a triplet gestation as Triplet I at 36 weeks of gestation via elective cesarean section. Birth weight was 1780 g (<3rd percentile), length 38.5 cm (<3rd percentile), and the general condition was assessed as 6 points on the Apgar scale.

The mother's multiple pregnancy was complicated by threatened preterm labor, cholestasis, and anemia. Prenatal ultrasound raised suspicion of chondrodysplasia and intrauterine growth restriction (IUGR) in one of the fetuses. Triplets II and III demonstrated normal body proportions and no other abnormalities.



Figure 2 Patient (IV:1) aged 18 with 3M syndrome.

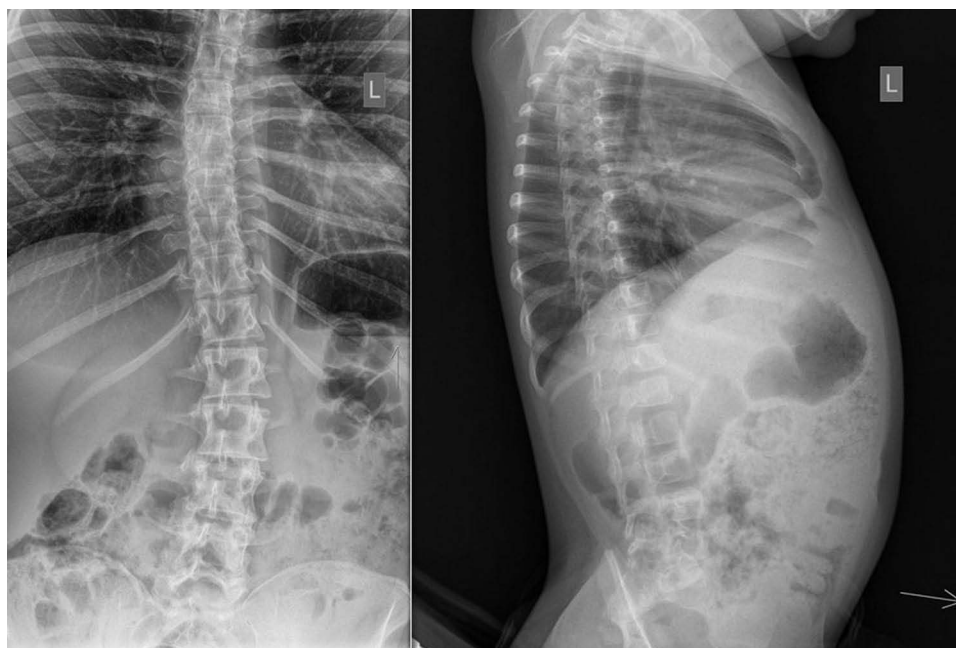


Figure 3 X-ray of the patient (IV:I): Thoracolumbar scoliosis with torsion of the vertebrae and their wedging in the thoracic spine. Increased height of the vertebrae in the lumbar spine and reduced anteroposterior dimension in the cross-section of the vertebrae.

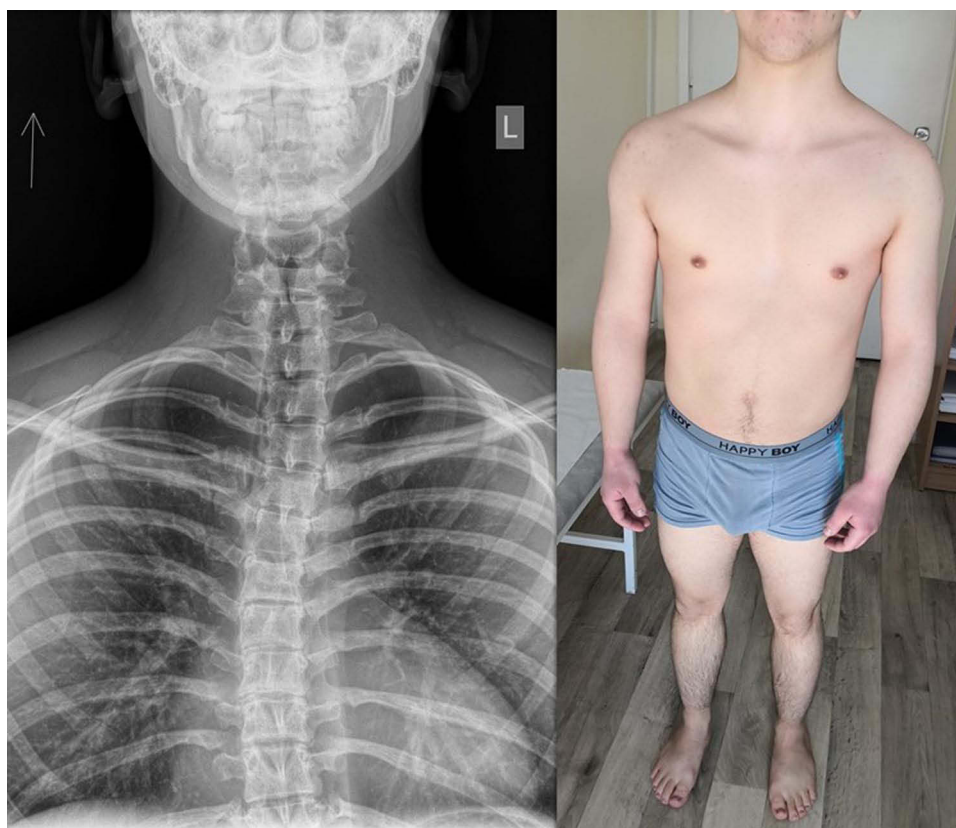


Figure 4 Patient of the patient (IV:I) and chest X-ray: short chest with funnel-shaped sternum, flat cross-section, and reduced curves.



Figure 5 X-ray of the patient (IV:1) narrow pelvis with reduced size of pubic bones. Spine with features of growth cartilage disorders.

After birth, the female infant was diagnosed with intrauterine hypotrophy and disproportional body features, including a distended abdomen, narrow thorax, short limbs, and a large triangular-shaped neurocranium. [Figure 6](#).

Newborn screening for metabolic disorders and hearing assessment were within normal limits. Head circumference was 34.5 cm, chest circumference 25 cm and body length 38.5 cm.

At 20 months of age, clinical examination revealed low body weight (<3rd percentile), increased head circumference (>97th percentile), elongated skull with a broad, prominent forehead, triangular face, slight hypotelorism with a midline flat hemangioma, a saddle-shaped nose with a fleshy tip, narrow thorax with a prominent sternum, a distended abdomen,



Figure 6 Patient (IV:3) aged 10 weeks with 3M syndrome.

large hands, and prominent heels. **Figure 7**. The child was not walking independently at the time of the examination. At 4 years of age, the biological age was delayed by 6 months.

An orthopedic examination revealed delayed motor development, preserved limb proportions with symmetrical mobility, and slight cervical hypotonia. The postural assessment showed a tendency toward trunk axis deviation.

Radiographic imaging demonstrated a long-arc spinal curvature with its apex at Th8–Th9, horizontally oriented slender ribs, and no distinct dysmorphic changes at this stage of development. The pelvis was narrow, with mild hip dysplasia. Due to the incomplete development of the skeletal system, periodic orthopedic and radiological follow-up was recommended. The child began walking independently after the age of two. Intellectual development is within normal limits.

At age four, the child presented with short stature (<3rd percentile), macrocephaly (>97th percentile), a triangular face with a sad expression, prominent lips, flattened zygomatic bones, and downward-slanting palpebral fissures. **Figure 8**. Additionally, generalized joint hypermobility and genu valgum were observed. Radiographic findings included horizontally oriented ribs, a narrow pelvis with reduced pubic bone size, and valgus deformity of the knees. **Figures 9 and 10**.

Methods

Peripheral blood samples were collected from the patients and family members.

aCGH was conducted using a commercially available array (CytoSure, Constitutional v3 (8x60k), Oxford Gene Technology (OGT), Oxfordshire, UK), according to the manufacturer's protocol. The CytoSure Interpret Software (OGT) was used for genomic copy-number analysis.

Next-generation sequencing (NGS). Whole exome sequencing (WES) was performed on the proband using Twist Human Core Exome Plus Kit (Twist Bioscience) and sequenced with Illumina technology (100x depth of mean coverage). Reads were aligned to the hg38 (GRCh38) reference genome. The obtained QC value was <99% for Q30. Alignment and variant calling were performed with an in-house bioinformatics pipeline. The identified variants were annotated using the Ensembl VEP and multiple databases, including ClinVar, dbSNP, HGMD, GnomAD. XHMMv1.0 algorithm and in-house scripts were used to search for small, rare copy number variants (CNVs). The American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines for the interpretation of sequence variants were followed in this study.⁹



Figure 7 Patient (IV:3) aged 20 months with 3M syndrome.

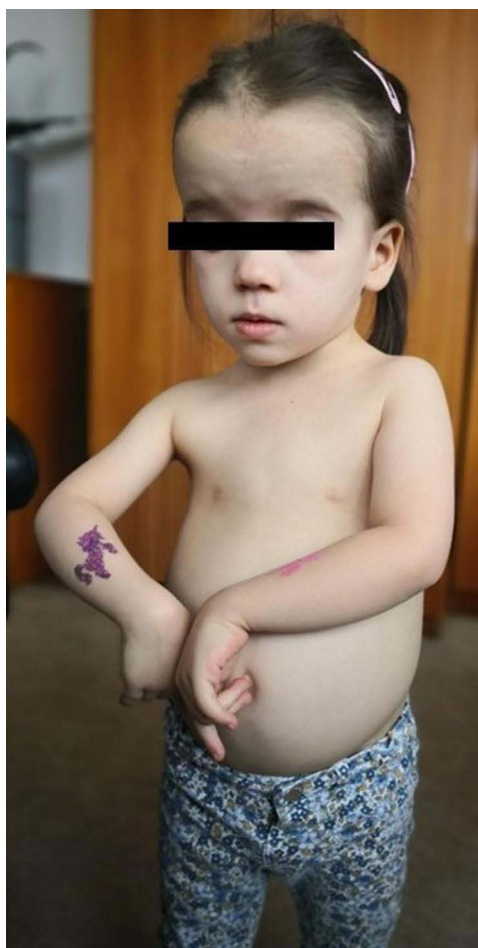


Figure 8 Patient (IV:3) aged 4 years and 7 months.

The presence of variants detected by next-generation sequencing was confirmed by Sanger sequencing. Additionally, Sanger sequencing was performed for the patient's family (parents and siblings).

The skeletal assessment and bone age were based on radiographic examination and compared with norms for the patient's age and gender. Vertebral body heights were measured along their longitudinal axis and in the lateral projection. Vertebral body widths were measured in the anteroposterior (AP) or posteroanterior (PA) projection. Lordosis angles were measured in the cervical and lumbar spine, and kyphosis angles in the thoracic spine.

Results

Due to the presenting symptoms, molecular testing was performed in patient IV:1 during infancy. Firstly, diagnostic testing was performed to detect common variants in the *FGFR3* gene (NM_000142.4): c.1138G > A and c.1138G > C (exon 10), associated with achondroplasia, as well as c.1620C > G and c.1620C > A (exon 14), associated with hypochondroplasia. No pathogenic variants were identified. Additionally, a normal constitutional karyotype of 46, XY was obtained.

In patient IV:3, molecular karyotyping using array comparative genomic hybridization (aCGH) from peripheral blood lymphocytes revealed no genomic imbalances in the analyzed regions.

Subsequently, whole exome sequencing (WES) was performed, with variant analysis focused on genes associated with the observed clinical phenotype, including skeletal dysplasias, facial dysmorphism, and limb shortening. A homozygous variant c.3523C > T (p.His1175Tyr) in the *CUL7* gene was identified. Variant has been reported in ClinVar as VUS (based on the single submission). This variant was absent in control chromosomes in GnomAD project (v3 and v4).

It has been submitted to the Leiden Open Variation Database (LOVD) under the ID CUL7:0000931619.



Figure 9 X-ray of the patient (IV:3): horizontal ribs, narrow pelvis with reduced size of pubic bones.



Figure 10 X-ray of the patient (IV:3): knee valgus.

Additional variants of uncertain significance were detected but are not detailed in this report due to the current lack of data regarding their pathogenicity and correlation with the patient's phenotype (data not shown). No CNVs were identified.

The presence of the c.3523C > T (p.His1175Tyr) variant in the *CUL7* gene was confirmed by Sanger sequencing using a second, independent blood sample from the affected girl (IV:3), her older brother (IV:1), who had previously been clinically diagnosed with 3M syndrome, and their healthy parents. Sanger sequencing confirmed the homozygous presence of the variant in both siblings and the heterozygous presence in both parents (III:4, III:5).

Considering the patient's and family's clinical data, the variant was classified as likely pathogenic, as it fulfills the ACMG criteria: PP1 (co-segregation with disease in affected family members), PP4 (patient's phenotype is highly specific for a disease), PM3 (for recessive disorder, variants detected in homozygous state), and PM2 (absent in population databases).

Discussion

Understanding disease pathogenesis and establishing genotype-phenotype correlations is essential for developing effective therapeutic strategies.^{1,9} Modern high-throughput genomic DNA analysis in patients presenting with clinical features of rare diseases enables the identification of novel genetic factors and additional variants in genes with confirmed clinical relevance. Previously, the diagnosis of 3M syndrome was based on the presence of characteristic clinical and radiological features.^{10–12} However, although these abnormalities are typical of 3M syndrome, they are not diagnostic, as similar radiographic changes can also be observed in other growth-related syndromes.^{5,10,13} Currently, the identification of biallelic pathogenic variants in *CCDC8*, *CUL7*, or *OBSL1* can confirm the disease and facilitate an earlier diagnosis, particularly when clinical and radiographic features are inconclusive.^{3,14} In patient IV:1, a clinical diagnosis of 3M syndrome was made at the age of 6; however, molecular confirmation of the diagnosis occurred only at the age of 18, following the diagnosis of the younger sister (IV:3).

Establishing a diagnosis is further complicated by the fact that skeletal abnormalities of the spine, particularly in the lumbar region, such as tall vertebral bodies and reduced anteroposterior and transverse diameters, become more apparent with age.^{5,10,14} Takizaki et al described a case in which the major skeletal features of 3M syndrome were identified both prenatally and in the neonatal period, including elongated long bones and tall vertebral bodies. However, these features became less apparent by the age of two years.¹¹

Both siblings were found to carry likely pathogenic c.3523C > T (p.His1175Tyr) variant in a homozygous state in the *CUL7* gene. Pathogenic variants in *CUL7* account for approximately 77.5% of genetically confirmed cases and are associated with 3M syndrome type 1.^{3,15} 3M syndrome is characterized by severe pre- and postnatal growth retardation.^{3,11,16} According to observations by van der Wal et al, the final adult height in affected individuals ranges from 5 to 6 standard deviations below the mean, corresponding to approximately 120–130 cm.¹⁷ The described patient (IV:1) was treated with recombinant human IGF-1 (rhIGF1) until the age of 16 and achieved a final height of 155 cm (<3rd percentile). According to the same authors, growth hormone therapy in patients with 3M syndrome has shown variable efficacy.^{6,16,17} In a Tunisian cohort, among seven patients with 3M syndrome carrying pathogenic variants in the *CUL7* gene, a positive response to growth hormone therapy was observed in only one case.⁶ *CUL7* is involved in chondrocyte growth and proliferation. Pathogenic variants in this gene impair the ability of the cullin-7 protein to interact with components of the ubiquitin–proteasome system, which is responsible for the degradation of unwanted proteins.^{6,15} In 3M syndrome, reduced cellular mitosis during early pregnancy may contribute to growth restriction, while impaired ubiquitination may play a role in the pathogenesis of IUGR.^{6,15,18} Moreover, *CUL7* pathogenic variants may disrupt insulin-like growth factor 1 (IGF-1) and growth hormone (GH) signaling pathways, further contributing to impaired growth.^{16,18}

Both siblings presented with IUGR and low birth weight. In the case of the girl, IUGR was more pronounced due to a triplet pregnancy. Infants from multiple pregnancies are generally smaller than singletons and represent a naturally occurring model of IUGR.¹⁹ Previously reported cases of children with 3M syndrome exhibited prenatal growth restriction and low postnatal weight. Growth delay persisted throughout childhood and adolescence, ultimately resulting in short adult stature.⁶ Moreover, patients described in the literature, similar to the siblings presented here, showed joint hypermobility, an increased risk of hip dislocation, and abnormal spinal curvature, such as kyphoscoliosis or hyperlordosis.^{3,6,18,20,21}

IUGR is associated with an increased risk of a range of adult-onset diseases, including cardiovascular disorders, obesity, and type 2 diabetes.^{22,23} It remains unclear whether the long-term health consequences of prematurity and IUGR will be the same for the brother, born from a singleton pregnancy, as for the sister, who was part of a multiple pregnancy.

Both siblings exhibited dysmorphic features characteristic of 3M syndrome; however, similar features are also present in several other conditions, such as Silver–Russell syndrome (SRS). SRS shares many similarities with 3M syndrome, including IUGR, short adult stature, a triangular face, relatively large head, asymmetry of the trunk or limbs, and clinodactyly.^{2,3,6} In contrast to 3M syndrome, SRS is associated with mild developmental delay but lacks skeletal abnormalities.^{3,6,11} According to numerous reports, 3M syndrome should always be considered in the differential diagnosis of patients presenting with prenatal growth retardation.^{3,11,15}

The identification of novel variants in relevant genes has expanded the known spectrum of changes involved in the pathogenesis of 3M syndrome. Moreover, the widespread sharing of data on known variants, combined with detailed clinical information, may, in the future, contribute to the development of a predictive model for genotype-phenotype correlation, as well as to the establishment of effective therapeutic strategies. Identification of a pathogenic variant in a family also allows direct diagnostics to exclude or confirm the disease in the fetus using traditional invasive prenatal diagnosis. It is also possible to use an alternative method, Preimplantation Genetic Diagnosis (PGD), after in vitro fertilization, which prevents pregnancy if a pathogenic variant is detected in the embryo.⁸ Fetal diagnosis is possible in families with a previously identified pathogenic variant causing this syndrome. In the described case, the diagnosis, supported by genetic testing, was made after the birth of another child, who was born from a multiple pregnancy (triplet), which could also have caused the observed symptoms. The prognosis for 3M syndrome is usually good and not life-threatening. It is an autosomal recessive disorder, with a 25% risk of recurrence in subsequent children. After diagnosis of 3M syndrome, the child should be followed by a pediatric endocrinologist to monitor growth and puberty and consider growth hormone therapy. Growth monitoring every 6–12 months is recommended until final height is achieved. Hip ultrasound should be performed in newborns to detect hip dysplasia. Patients should be under the ongoing care of an orthopedist. Assistive devices for short stature and physical therapy should also be considered. Semen analysis should also be discussed and offered to male patients near the end of puberty.^{8,11,15}

Conclusion

The expansion of the database of genetic variants, combined with knowledge of the spectrum and severity of a patient's clinical manifestations, enables the identification of genotype-phenotype correlations that are crucial for medical care.

Abbreviations

ACMG, American College of Medical Genetics and Genomics; C, centyl; *FGFR3*, Fibroblast Growth Factor Receptor 3; GH, growth hormone; IGF-1, insulin-like growth factor 1; IUGR, Intrauterine Growth Restriction; LOVD, Leiden Open Variation Database; L, lumbar spine; 3M, Miller-McKusick-Malvaux syndrome; NGS, Next-generation sequencing; OGT, Oxford Gene Technology; OMIM, Online Mendelian Inheritance in Man; rhIGF1, human insulin-like growth factor; PGD, Preimplantation Genetic Diagnosis; SD, standard deviation; Th, thoracic spine; WES, Whole exome sequencing.

Ethics Disclosure

The study was performed in accordance with the Declaration of Helsinki and accepted standards of ethics. This study has been reviewed and approved by NCU Committee of Bioethics KB 371/2023. The consent of the relevant bioethics committee was obtained: Bioethics Committee of Nicolaus Copernicus University, Toruń, Poland. NCU Committee of Bioethics KB 371/2023.

Consent

All patients signed written informed consent to take part in the study. In the case of children, written consent for the part in the study was signed on the study by the parents. All patients signed written informed consent for the publication of their clinical data. In the case of children, written consent for publication was obtained by the parents. All patients signed written informed consent to use their photographs. In the case of children, written consent to use photos was obtained

from parents. I confirm that all living family members included in the pedigree have been informed of this publication and have given their consent to include their data.

Acknowledgments

We would like to thank the patient and parents for the opportunity to use the photos for this article.

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.

Funding

The author(s) received no financial support for this article's research, authorship, and/or publication.

Disclosure

The authors declare that they have no competing interests.

References

1. El Naofal M, Ramaswamy S, Alsarhan A, et al. The genomic landscape of rare disorders in the Middle East. *Genome Med.* 2023;15(1). doi:10.1186/s13073-023-01157-8.
2. Güven A, Cebeci AN. 3M syndrome: a report of four cases in two families. *J Clin Res Ped Endo.* 2011;3:154–159.
3. Elsayed S, Elmakkawy G, Abdelrazek I, et al. An update on 3M syndrome: review of clinical and molecular aspects and report of additional families. *Am J Med Genet.* 2024;194. doi:10.1002/ajmg.a.64068
4. HabibUllah H, Al-Baradie R, Bashir S. 3-M syndrome: a local case report. *Am J Case Rep.* 2019;20:36–38. doi:10.12659/AJCR.912736
5. Huber C, Delezoide AL, Guimiot F, et al. A large-scale mutation search reveals genetic heterogeneity in 3M syndrome. *Eur J Hum Genet.* 2009;17:395–400. doi:10.1038/ejhg.2008.200
6. Shaikh S, Shettigar SKG, Kumar S, et al. Novel mutation in *Cul7* gene in a family diagnosed with 3M syndrome. *J Genet.* 2019;98:1–5. doi:10.1007/s12041-019-1057-6
7. Sommariva E, Bellin M, Di Resta C. Advance in genomics of rare genetic diseases. *Biomolecules.* 2023;13:1441. doi:10.3390/biom13101441
8. Pasińska M, Łazarczyk E, Jułga K, Bartnik-Głaska M, Nowakowska B, Haus O. Multiple occurrence of psychomotor retardation and recurrent miscarriages in a family with a submicroscopic reciprocal translocation t(7;17)(p22;p13.2). *BMC Med Genomics.* 2018;11(11):69–75. doi:10.1186/s12920-018-0384-4
9. Richards S, Aziz N, Bale S, ACMG Laboratory Quality Assurance Committee, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 17;2015:405–424. doi:10.1038/gim.2015.30
10. 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(148):–153. doi:10.1016/j.ajhg.2011.05.028
11. Takizaki N, Tsurusaki Y, Katsumata K, et al. Novel *CUL7* biallelic mutations alter the skeletal phenotype of 3M syndrome. *Hum Genome Var.* 2020;7:1–3. doi:10.1038/s41439-020-0090-6
12. Al-Dosari MS, Al-Shammari M, Shaheen R, et al. 3M syndrome: an easily recognizable yet underdiagnosed cause of proportionate short stature. *J Pediatr.* 2012;161:139–145. doi:10.1016/j.jpeds.2011.12.051
13. Jacob P, Girisha KM. Three M syndrome 2 in two Indian patients. *Am J Med Genet.* 2021;185A:614–616. doi:10.1002/ajmg.a.61949
14. Kumar MH, Kumar MS, Kumar VS, et al. An adult with 3-M syndrome. *BMJ Case Rep.* 2015;2015:bcr2015211429. doi:10.1136/bcr-2015-211429
15. Invitto S, Grasso A, Lofrumento DD, et al. Chemosensory event-related potentials and power spectrum could be a possible biomarker in 3M syndrome infants? *Brain Sci.* 2020;10(4):201–214. doi:10.3390/brainsci10040201
16. Yan J, Yan F, Li Z, et al. The 3M complex maintains microtubule and genome integrity. *Mol Cell.* 2014;54:791–804. doi:10.1016/j.molcel.2014.03.047
17. van der Wal G, Otten BJ, Brunner HG, et al. 3-M syndrome: description of six new patients with review of the literature. *Clin Dysmorphol.* 2001;10:241–252. doi:10.1097/00019605-200110000-00002
18. Wang P, Yan F, Li Z, et al. 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
19. Khalil A, Townsend R. Fetal growth restriction in twins. *Best Pract Res Clin Obstet Gynaecol.* 2018;49:79–88. doi:10.1016/j.bpobgyn.2018.02.004
20. Aldhoon-Hainerova I, Baranowski E, Kinning E, et al. Gonadal failure in a male with 3-M syndrome. *JCEM Case Rep.* 2024;2. doi:10.1210/jcemcr/luae084
21. Xu N, Liu K, Yang Y, et al. Chinese patients with 3M syndrome: clinical manifestations and two novel pathogenic variants. *Front Genet.* 2023;31(14):1164936. doi:10.3389/fgene.2023.1164936

22. Muhlhauser BS, Hancock AN, Bloomfield FH, et al. Are twins growth restricted? *Pediatr Res.* 2011;70:117–122. doi:10.1203/PDR.0b013e31821f6cfd
23. Essaddam L, Becher SB. 3M syndrome: a rare cause of short stature. *Indian Pediatr.* 2019;56:799. doi:10.1007/s13312-019-1632-1

The Application of Clinical Genetics

Dovepress
Taylor & Francis Group

Publish your work in this journal

The Application of Clinical Genetics is an international, peer-reviewed open access journal that welcomes laboratory and clinical findings in the field of human genetics. Specific topics include: Population genetics; Functional genetics; Natural history of genetic disease; Management of genetic disease; Mechanisms of genetic disease; Counselling and ethical issues; Animal models; Pharmacogenetics; Prenatal diagnosis; Dysmorphology. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/the-application-of-clinical-genetics-journal>