# First documented case of Myhre syndrome in Romania: A case report

ANDREEA CĂTANĂ[1-3], RUXANDRA SIMONESCU-COLAN[1], ZINA CUZMICI-BARABAȘ[2,3], DIANA MILITARU[2], IRINA IORDĂNESCU[3] and MARIELA SANDA MILITARU[2,3]

[1]Department of Oncogenetics, Institute of Oncology I. Chiricuță, 4000015 Cluj-Napoca; [2]Department of Molecular Sciences, University of Medicine and Pharmacy, 4000012 Cluj-Napoca; [3]Department of Medical Genetics, Genetic Center Laboratory, Regina Maria, 011376 Bucharest, Romania

Received October 4, 2021; Accepted November 3, 2021

DOI: 10.3892/etm.2022.11252

**Abstract.** Myhre syndrome is a rare genetic autosomal dominant connective tissue disorder, characterized by developmental delay, characteristic facial features, various bone and joint abnormalities, distinctive cardiovascular, ophthalmological and ear, nose and throat (ENT) manifestations, in association with mild to moderate intellectual disability and autism or autism spectrum disorder-like behaviour. The diagnosis of Myhre syndrome is established corroborating the clinical findings with *SMAD4* heterozygous mutation identified in the majority of the patients. *SMAD4* gene mutations result in abnormal TGF-β signalling in several cell types, which affects the development of several body systems and leads to the specific phenotype of Myhre syndrome. We herein report the case of an 18-year-old female patient who was diagnosed at the age of 17 years with Myhre syndrome, the first documented case of this syndrome in Romania. Sequence analysis of protein-coding genes using whole-exome analysis identified a '*de novo*', heterozygous missense variant of *SMAD4*, c.1498A>G, p. (Ile500Val), which is pathogenic for Myhre syndrome. Although this condition is rare, a series of particularities were identified in the present case, consisting of severe allergic reactions, recurrent ENT tumour development and delayed dental eruption, which have not been described in Myhre syndrome to date, to the best of the authors' knowledge.

## Introduction

Myhre syndrome (Online Mendelian Inheritance in Man entry no. 139210), first observed in 1981 (1), has thus far been reported in <100 patients worldwide (2). Myhre syndrome is an autosomal dominant connective tissue disorder affecting patients from a young age without ethnic or sex predilection. Clinical manifestations include intrauterine growth retardation, short stature and limited joint mobility (3). More common phenotypical traits become recognizable in childhood, including distinct facial dysmorphic features, such as midface hypoplasia, short palpebral fissure, narrow mouth and prognathism, smaller dysplastic ears, brachydactyly and clinodactyly with hyperconvex nails. Thick skin and atypical scarring are also documented in most cases (4). These patients usually present with hearing loss, ophthalmological manifestations, the most common being strabismus (5). Different cardiovascular and respiratory manifestations, including heart failure and dyspnoea (6) due to septal defects, aortic defects or laryngotracheal stenosis, may also be observed, some of which may be life-threatening, while limited intellect and autism spectrum disorder-like behaviour may affect the capability of having normal social interactions (7).

The diagnosis of Myhre syndrome is quite challenging, and it is based on characteristic clinical and imaging features and confirmed by specific molecular diagnosis.

The most common aetiology is a heterozygous mutation in the *SMAD4* gene affecting the codon for Ile500, which encodes a tumour-suppressor protein. Thus, the TGF-β signalling pathway is affected owing to the aforementioned manifestations (8). In most reported cases, the mutation appears *de novo* (9). A small number of Myhre syndrome diagnoses have been associated with *SMAD4* missense mutation causing the replacement of Arg496 (10).

## Case report

The case reported in the present study involves an 18-year-old female patient presenting with short stature, facial deformities, chronic muscle and joint pain, multiple allergies and suspicion of vasculitis, without diagnosis of any autoimmune diseases, and with a predisposition for developing recurring choanal benign tumours causing severe nasal obstruction, dizziness and headaches, severely affecting daily activities. Due to the heterogeneity of symptoms, diagnosis was delayed and the patient was finally diagnosed with Myhre syndrome following whole-exome sequencing (WES) molecular analysis.

*Correspondence to:* Dr Andreea Cătană, Department of Oncogenetics, Institute of Oncology I. Chiricuță, 34-36 Strada Republicii, 4000015 Cluj-Napoca, Romania
E-mail: catanaandreea@gmail.com

*Key words:* Myhre syndrome, *SMAD4* gene, whole-exome sequencing, ear, nose and throat infections, allergic manifestations

The patient, who is the first documented case of Myhre syndrome in Romania, was diagnosed at the age of 17 years. The patient was born by caesarean section after a pregnancy associated with multiple episodes of first-trimester haemorrhage. Both parents were aged 35 years at the time of the patient's birth. The patient exhibited mild intrauterine growth retardation and microcephaly. Slower weight gain and orthopnoea were observed from the early neonatal period The patient also exhibited delayed dental eruption, having the first teeth at 18 months of age (normal range, 6-8 months); there were no observed dental abnormalities.

Since the age of 18 months, the patient developed several severe allergic reactions to insect bites, which required hospitalizations and steroid treatment. By the age of 3 years, the patient was suffering from recurrent ENT infections and vocal cord nodules causing hoarseness, which resolved spontaneously after 1 year. At 10 years of age, the patient underwent an adenoidectomy. The chronic muscle and joint pains were not associated with any neurological findings.

The patient exhibited a short stature at 152 cm (mother: 178 cm, father: 182 cm), lumbar lordosis, thickened calvarium and facial deformities, including maxillary hypoplasia, large forehead, microstomia, thin upper lip, prominent nasal root, narrow palpebral fissures and strabismus. The skin on the palms and feet was thickened and stiff, and there were multiple stretch marks and abnormal scarring on different parts of the body. Brachydactyly, camptodactyly and clinodactyly were also be observed in the hands. A routine clinical check-up followed by ultrasound imaging revealed the presence of mild coarctation of the aorta, in the absence of hemodynamically significant alterations (Fig. 1).

By the time of diagnosis, the patient had developed facial tics, chronic constipation (despite a healthy, well-balanced diet) and severe menstrual abnormalities (dysmenorrhea and oligomenorrhea), which were corrected to a certain extent with medication (oestrogen and progesterone).

Immediately prior to recommending genetic testing, the patient presented with severe nasal obstruction, dizziness and severe headaches. The ENT clinical and MRI examinations revealed a bilateral circumferential choanal tumour, with a suspected diagnosis of rhinoscleroma, or post-adenoidectomy stenosis. Surgery was performed under general anaesthesia with orotracheal intubation, with an apparent favourable postoperative evolution. By the age of 12 years, the surgical follow-up showed signs of recurrence and further investigations have been advised, but have not been performed due to the patient's altered emotional status at the time. Three months later, in the context of the patient's ENT symptomatology, audiometry was also performed, revealing conductive hearing loss.

Routine check-up urinalysis revealed haematuria, leukocyturia and proteinuria, leading to the diagnosis of nephrotic syndrome. Corroborated with a lack of determined aetiology for the ENT manifestations, vasculitis was suspected. The absence of symptoms suggesting an autoimmune systemic inflammatory process and the results of paraclinical investigations (negative inflammatory markers, negative antineutrophil cytoplasmic antibodies and anti-C1q serology) excluded the presumed diagnosis.

The ophthalmological evaluation revealed esophoria, pseudopapillitis, myopia and astigmatism. The recommended MRI examination for the evaluation of the optic nerve revealed no pathological findings (Table I).

Given the phenotype of the patient and the lack of similar clinical manifestations in other family members, after informed consent was obtained from both the patient and her parents, WES was performed. Sequence analysis of all protein-coding genes using the Whole Exome Plus test (Blueprint Genetics) identified a heterozygous missense variant of *SMAD4* c.1498A>G, p. (Ile500Val), which is pathogenic for Myhre syndrome. The test was associated with whole exome deletion/duplication (copy number variation) analysis, which came back negative. The patient was also tested for secondary findings, whole-exome data being analysed in 59 genes following the recommendations of the American College of Medical Genetics and Genomics (11). No other abnormalities were identified in the genetic analyses. The patient's father was diagnosed with multiple rectocolic micropolyps and was also tested for the *SMAD4* mutation, as an association was suspected, but the results of the genetic test were negative. As the patient's mother was asymptomatic, she was not tested for the mutation identified in the proband.

## Discussion

Diagnosis of rare diseases is often challenging, particularly when there is no family history, and the symptoms are heterogeneous and do not fall within a characteristic phenotypic spectrum.

In Myhre syndrome, symptoms tend to go unnoticed in early childhood and become noticeable in adolescence, as in the present case. Diagnosing the condition was even more challenging, as there is no other case of Myhre syndrome reported in Romania. After several seemingly unrelated symptoms and several medical consults, molecular diagnosis was performed using WES, identifying the mutation in the *SMAD4* gene.

The key element in Myhre syndrome is the TGF-β signalling pathway that controls important biological cell processes, including cell proliferation, apoptosis and cell lineage coordination. As *SMAD4* represents a coactivator of TGF-β, dysregulation of *SMAD4* function has pleiotropic effects, which are in line with the major features of Myhre syndrome resulting from the perturbation of the developmental pathways controlled by TGF-β/bone morphogenetic protein signalling during embryonic development, including skeletal axis patterning, tissue specification and organogenesis. The most common molecular defect in Myhre syndrome is represented by the restricted 3 amino acid spectrum of Ile500 mutations (threonine, valine and methionine) found in almost all patients, albeit with no clear genotype-phenotype correlations (9).

Recurrent ear infections possibly leading to hearing loss were previously reported in several patients with Myhre syndrome (11). *SMAD4* gene mutations are known to be associated with tumorigenesis, as the mutated variant was identified in both malignant and benign lesions (12). However, the predisposition to developing ENT tumours has not yet been reported in Myhre syndrome, to the best of our knowledge. The patient reported in the present case exhibited severe nasal obstruction due to the development of bilateral circumferential choanal tumours, associated with dizziness and intense headaches, requiring surgical intervention. After the tumour was

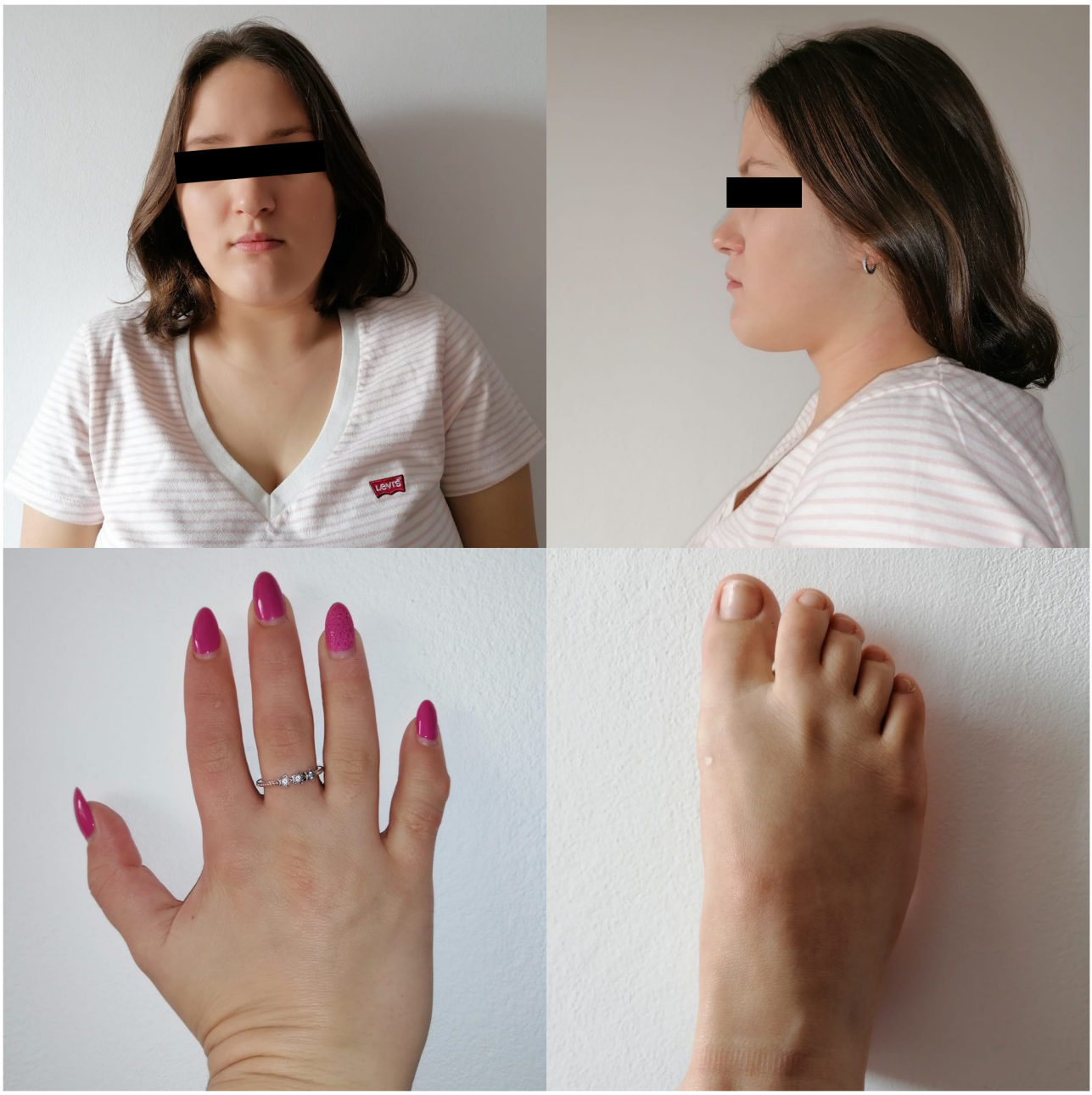

Figure 1. Morphological characteristics of Myhre syndrome in the present case. The patient exhibited characteristic morphological features of Myhre syndrome, including microcephaly, maxillary hypoplasia, large forehead, microstomia, thin upper lip, prominent nasal root and narrow palpebral fissures (upper panels), brachydactyly, camptodactyly and clinodactyly (lower panels).

removed, the patient's condition improved significantly, but further investigations showed early signs of recurrence.

Different skeletal abnormalities and facial deformities are often observed, and the developmental delay occurs in all Myhre syndrome patients (13). The particularity of our case is the delayed dental eruption: The first teeth appeared in our patient at 18 months of age, but no dental abnormalities were found otherwise.

The clinical picture of our patient is predominated by ENT-related pathology and severe allergic manifestations. The SMAD4 protein is an important mediator of TGF-β signalling, which is known to serve an important role in inducing and maintaining the inflammatory response, and its correlation with allergic asthma and immunomodulation has already been documented (12,13). Although allergic reactions have not been reported in Myhre syndrome patients to date (14), our patient experienced severe reactions to insect bites from a very young age and has a documented allergy to vitamin K, pollen, mould and other particles. The patient's symptoms have become milder over time, but she required several hospitalizations and corticosteroid treatment due to severe allergic reactions during childhood.

As in the present case, patients with Myhre syndrome develop this disorder due to a *de novo SMAD4* pathogenic variant. According to *SMAD4* expression in the phenotype, Myhre syndrome has a 50% recurrence risk, although fertility and reproduction have not been assessed. If the *SMAD4* pathogenic variant is absent in the parents, the

Table I. Clinical features of the present case in comparison with other reported cases of patients with Myhre syndrome.

| Phenotype in Myhre syndrome | Literature reports on Myhre syndrome phenotype | Patient phenotype | (Refs.) |
|---|---|---|---|
| Facial deformities | Microcephaly with thickened calvarium, narrowed palpebral fissures, midface hypoplasia, microstomia, prognathism, hypertelorism, prominent nasal root, cleft palate | Microcephaly, maxillary hypoplasia, large forehead, microstomia, thin upper lip, prominent nasal root, narrow palpebral fissures | (1,2) |
| Height, weight and developmental abnormalities | Short stature, obesity | Short stature (152 cm), delayed dental eruption, intrauterine growth retardation | (1-3) |
| Osteoarticular abnormalities | Limited joint mobility, thick calvaria, short neck, broad ribs, brachydactyly, camptodactyly, clinodactyly | Brachydactyly, camptodactyly, clinodactyly, chronic muscle and joint pain | (1-3) |
| Muscular hypertrophy | + | - | |
| Neurological involvement | Seizures, mental retardation, cerebral ataxia | Facial tics | (1,2) |
| Cardiovascular involvement | Septal defects, aortic stenosis, aortic coarctation, pericardial effusion, pericardial fibrosis | Aortic coarctation, mitral valve regurgitation | (2) |
| Respiratory tract involvement | Laryngotracheal stenosis, respiratory failure, dyspnea | Orthopnea | (2) |
| Ear, nose and throat involvement | Early-onset mixed conductive and sensorineural deafness, voice abnormalities (hoarseness, nasal voice) | Vocal cord nodules, hoarseness, hearing loss, recurring bilateral choanal tumor | (1,3) |
| Genito-urinary involvement | Cryptorchidism, menstrual abnormalities (oligomenorrhea, metrorrhagia), vesicoureteral reflux, primary enuresis | Menstrual irregularities (oligomenorrhea) | |
| Gastroenterological involvement | Severe constipation | Chronic constipation | (4) |
| Skin hypertrophy | Skin thickening and stiffness | Thickened skin, abnormal scarring, stretch marks | (2) |
| Ophthalmological involvement | Strabismus, astigmatism, pseudopapillitis | Esophoria, pseudopapillitis, myopia, astigmatism | (1,2) |
| Immunological involvement | - | Multiple allergies | |

risk to sibs is presumed to be slightly higher compared with that of the general population, but <1% as a possibility of parental germline mosaicism; therefore, if a *SMAD4* pathogenic variant has been identified in an affected family member, prenatal testing or preimplantation genetic testing can be recommended.

In conclusion, Myhre syndrome is a rare autosomal dominant connective tissue disorder caused by a germline mutation in the *SMAD4* gene. Common signs include short stature, skeletal abnormalities, limited joint mobility, characteristic facial features, intellectual and behavioural abnormalities. We herein report the case of an 18-year-old female patient with short stature, brachydactyly/clinodactyly, facial dysmorphia, thickened skin, ENT complications, coarctation of the aorta and *SMAD4* c.1498A>G, p. (Ile500Val) mutation, with a late diagnosis. An atypical finding in the present case was severe allergies. Although the patient's clinical symptoms are chronic and persistent, the major discomfort is mental. The late diagnosis, lack of medical information, as well as the lack of adequate medical knowledge have led to generalized anxiety that ultimately required psychological intervention.

The current case report is proof that a multidisciplinary approach is essential for the diagnosis of rare genetic diseases. Phenotype heterogeneity requires, in most cases, extensive molecular testing in order to reach a definitive diagnosis.

**Acknowledgements**

Not applicable.

**Funding**

No funding was received.

## Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

## Authors' contributions

AC and MSM performed genetic consult and counselling; II, AC and ZCB have seen and confirm the authenticity of the raw data; DM and RSC performed the interpretation of genetic test results. All the authors have read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

The patient provided written consent for the publication of the case details and any associated images.

## Competing interests

The authors declare that they have no competing interests.

## References

1. Myhre SA, Ruvalcaba RH and Graham CB: A new growth deficiency syndrome. Clin Genet 20: 1-5, 1981.
2. Caputo V, Bocchinfuso G, Castori M, Traversa A, Pizzuti A, Stella L, Grammatico P and Tartaglia M: Novel SMAD4 mutation causing Myhre syndrome. Am J Med Genet A 164A: 1835-1840, 2014.
3. Caputo V, Cianetti L, Niceta M, Carta C, Ciolfi A, Bocchinfuso G, Carrani E, Dentici ML, Biamino E, Belligni E, *et al*: A restricted spectrum of mutations in the SMAD4 tumor-suppressor gene underlies Myhre syndrome. Am J Hum Genet 90: 161-169, 2012.
4. Asakura Y, Muroya K, Sato T, Kurosawa K, Nishimura G and Adachi M: First case of a Japanese girl with Myhre syndrome due to a heterozygous SMAD4 mutation. Am J Med Genet A 158A: 1982-1986, 2012.
5. Starr LJ, Lindor NM and Lin AE: Myhre Syndrome. In: GeneReviews®. University of Washington, Seattle, Seattle WA, 2017. https://www.ncbi.nlm.nih.gov/books/NBK425723/.
6. Titomanlio L, Marzano MG, Rossi E, D'Armiento M, De Brasi D, Vega GR, Andreucci MV, Orsini AV, Santoro L and Sebastio G: Case of Myhre syndrome with autism and peculiar skin histological findings. Am J Med Genet 103: 163-165, 2001.
7. Michot C, Le Goff C, Mahaut C, Afenjar A, Brooks AS, Campeau PM, Destree A, Di Rocco M, Donnai D, Hennekam R, *et al*: Myhre and LAPS syndromes: Clinical and molecular review of 32 patients. Eur J Hum Genet 2: 1272-1277, 2014.
8. Whiteford ML: Myhre Syndrome. In: NORD Guide to Rare Disorders. Lippincott Williams & Wilkins. Philadelphia, PA, p225, 2003.
9. Lazzereschi D, Nardi F, Turco A, Ottini L, D'Amico C, Mariani-Costantini R, Gulino A and Coppa A: A complex pattern of mutations and abnormal splicing of Smad4 is present in thyroid tumours. Oncogene 24: 5344-5354, 2005.
10. Le Goff C, Michot C and Cormier-Daire V: Myhre syndrome. Clin Genet 85: 503-513, 2014.
11. Miller DT, Lee K, Chung WK, Gordon AS, Herman GE, Klein TE, Stewart DR, Amendola LM, Adelman K, Bale SJ, *et al*: ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med 23: 1381-1390, 2021.
12. Tirado-Rodriguez B, Ortega E, Segura-Medina P and Huerta-Yepez S: TGF-β: An important mediator of allergic disease and a molecule with dual activity in cancer development. J Immunol Res 2014: 318481, 2014.
13. Garavelli L, Maini I, Baccilieri F, Ivanovski I, Pollazzon M, Rosato S, Iughetti L, Unger S, Superti-Furga A and Tartaglia M: Natural history and life-threatening complications in Myhre syndrome and review of the literature. Eur J Pediatr 175: 1307-1315, 2016.
14. McGowan R, Gulati R, McHenry P, Cooke A, Butler S, Keng WT, Murday V, Whiteford M, Dikkers FG, Sikkema-Raddatz B, *et al*: Clinical features and respiratory complications in Myhre syndrome. Eur J Med Genet 54: e553-e559, 2011.