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Spectrum of Congenital Anomalies in Myhre Syndrome—Insights Into Effects Brought by Altered TGF-β Signaling via Gain-of-Function Variants in *SMAD4*

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ABSTRACT

Myhre syndrome is a rare genetic disorder characterized by progressive multisystem involvement. Gain-of-function missense heterozygous variants affecting the Ile500 residue and Arg496 residue of the *SMAD4* gene are implicated in this condition. In this article, we aim to understand the spectrum of congenital anomalies in Myhre syndrome by studying a cohort of previously unreported patients alongside published literature. Our analysis revealed that the musculoskeletal system was the most common system to be affected, followed by the cardiovascular system. Intrauterine growth restriction was the most reported intrauterine anomaly. Although there was no clear genotype–phenotype correlation, it appears that the Ile500Thr variant showed early multisystem involvement compared to other variants.

1 | Introduction

Myhre syndrome (MIM #139210) is a rare genetic disorder characterized by short stature, distinctive facial appearance and progressive fibrosis in several systems of the body, namely, cardiovascular, musculoskeletal, respiratory, neurological, genitourinary, gastrointestinal, endocrinological and skin (Michot et al. 2014). Gain of function missense heterozygous variants affecting the Ile500 residue (amino acid changes to valine c.1498A>G [p.Ile500Val], threonine c.1499T>C [p.Ile500Thr], and leucine c.1498A>C [p.Ile500Leu]) and residue Arg496 (amino acid changes to cysteine c.1486C>T [p.Arg496Cys]) of the *SMAD4* gene are implicated in this condition (Le Goff et al. 2011; Caputo et al. 2014).

With advancing knowledge, improved technology, better access to testing and low threshold for genetic testing, Myhre Syndrome patients are increasingly being diagnosed at a young age (Lin et al. 2024). Therefore, understanding the spectrum of congenital anomalies in this ultra-rare disorder has become pivotal in offering early genetic testing, establishing an accurate diagnosis and optimizing the management of these patients. Herein, we explore the structural congenital anomalies (detected in utero or within 1 year of life) seen in patients with a confirmed molecular

diagnosis of Myhre syndrome by studying a previously unreported cohort of United Kingdom (UK) patients alongside those in the published literature.

2 | Methods

We included patients with a confirmed genetic diagnosis of Myhre Syndrome from two main sources:

1. Previously unreported UK patients: We identified patients with a molecularly confirmed diagnosis of Myhre Syndrome from the international database DECIPHER (https://www.deciphergenomics.org/), those diagnosed through the 100,000 genomes project (https://www.genomicsengland.co.uk/initiatives/100000-genomes-project), and the NHS Genomic Medicine Service (https://www.england.nhs.uk/genomics/nhs-genomic-med-service/). Patients were also recruited through the Myhre Syndrome UK and Europe Foundation (https://www.myhresyndrome.com/).

Those identified through DECIPHER had a molecular confirmation by exome sequencing, and those from the 100,000 genomes project and NHS Genomic Medicine Services had whole genome sequencing. The pipelines used for testing and analysis are detailed in previously published literature (Wright et al. 2015; Marx 2015). Details of the genotype and phenotype were gathered from the databases as well as by contacting the clinicians of the identified patients.

2. Previously published patients: For this cohort, PubMed and Google Scholar databases were searched with the keywords "Myhre syndrome" and "congenital anomalies." All patients described in the literature with a molecular confirmation of Myhre syndrome were included in the analysis. Publications which were not in English were excluded. Care was taken to avoid duplicating patient inclusion in cases where the information was published in more than one paper. This was achieved by carefully scrutinizing individual patient information presented in the Supporting Information of each publication. The number of patients included from each article is mentioned in the tables. We considered an anomaly to be "congenital" if it was detected in the intrauterine period or if it was detected within the first year of life. Other structural anomalies that were considered to be developmental but were diagnosed late (greater than 1 year) (for e.g., cleft palate) were also included as a congenital anomaly. In cases where the time of onset of the anomaly was not clear, for example, radiological abnormalities such as thickened calvarium, these were excluded from the analysis given that the frequency of skeletal surveys was not uniform among all the patients.

We used an organ-system approach to analyze the congenital anomalies data collected. Further, we looked for genotype–phenotype correlation by comparing the frequency, severity, and occurrence of rare anomalies in the four recurrent genotypes. Our analysis did not include data on dysmorphic features or growth at birth since this piece of information was not available in most cases.

3 | Results

We studied a total of 195 patients, including 185 patients already published in 42 publications and 10 new patients that we report for the first time. Among the published patients, gender was not specified in two publications (three patients), which were based on prenatal diagnosis of Myhre syndrome (Jury et al. 2024; Hui et al. 2023). In the remaining cohort, there was a slight preponderance of females, 108/192 (56.25%).

3.1 | Genotype

The predominant genotype in the cohort was c.1498A>G (p.Ile500Val), present in 109/195 (55.8%) patients. This was followed by the c.1486C>T (p.Arg496Cys) variant in 53/195 (27.2%) patients, and 30/195 (15.4%) patients had the c.1499T>C (p.Ile500Thr) variant. Only 3/195 (1.5%) had the c.1498A>C (Ile500Leu) variant.

Most cases of Myhre syndrome are de novo in origin. However, three families with familial recurrence of Myhre syndrome have been reported in the literature, where the variant was inherited from an affected parent. Interestingly, in all three families, the variant change was c.1486C>T (p.Arg496Cys) (Spineli-Silva et al. 2025, Demir et al. 2023, Meerschaut et al. 2019).

3.2 | Phenotype

Musculoskeletal system was the commonest (in 64%; 125/195) system to be affected congenitally, according to our analysis. The second commonest (in 29.2%; 57/195) congenital involvement was seen in the cardiovascular system; these had more serious clinical implications compared to most other systems' involvement and are hence described first.

3.2.1 | Cardiovascular Anomalies

Our analysis revealed that congenital anomalies of the cardiovascular system were common, affecting 80/195 (41%) patients.

The most prevalent anomaly was patent ductus arteriosus (26/80, 32.5%), followed by coarctation of aorta (19/80, 23.75%). Mitral stenosis and ventricular septal defect were seen in 13.75% (11/80) and 12.5% (10/80), respectively. Tetralogy of Fallot was observed in seven out of 80 patients (0.09%). Other structural abnormalities such as aortic stenosis, pulmonary valve stenosis, and atrial septal defect were less frequently reported. Shone's complex (supravalvular mitral ring, parachute mitral valve, subaortic stenosis, and aortic coarctation) was observed in two patients. At least 15 patients (15/80, 18.75%) had more than one cardiovascular abnormality, with the most frequent combination being coarctation of aorta with patent ductus arteriosus

TABLE 1 | Congenital anomalies of the cardiovascular system.

	Jury et al. (2024) (*n* = 2)	Vanbelleghem (2024) (*n* = 24)	Tayara et al. (2024) (1)	Lin et al. (2024) (*n* = 47)	Brunet-Garcia (2023) (*n* = 2)	Yang et al. (2022) (*n* = 12)	Cătană et al. (2022) (*n* = 1)	Cappuccio et al. (2022) (*n* = 5)	Kilci et al. (2022) (*n* = 1)	Jeon et al. (2021) (*n* = 1)	Lim et al. (2021) (*n* = 1)	Jensen et al. (2020) (*n* = 1)
Number of patients with a congenital cardiac abnormality	1	2	1	27	1	4	1	5	1	1	1	1
PDA				6		1			1	1	1	
Shone's complex						2						
VSD	1			3		1						
ASD				2								
AS												
PS				2								1
APV								2				
MS		1		10								
MI												
CA			1	4	1		1		1			
PAS		1								1		1
ToF								5				

	Varenyiova et al. (2020) (*n* = 1)	Li et al. (2020) (*n* = 2)	Meerschaut et al. (2019) (*n* = 4)	Yu et al. (2019) (*n* = 6)	Alagia et al. (2018) (*n* = 1)	Garavelli et al. (2016) (*n* = 1)	Lin et al. (2016) (*n* = 3)	Bassett et al. (2016) (*n* = 1)	Starr et al. (2015) (*n* = 5)	Michot et al. (2014) (*n* = 28)	Our cohort (*n* = 10)	Total
Number of patients with a congenital cardiac abnormality	1	1	3	3	1	1	2	1	2	17	2	80
PDA		1	1	3			1	1		8	1	26
Shone's complex												2

(Continues)

TABLE 1 | (Continued)

	Varenyiova et al. (2020) (*n* = 1)	Li et al. (2020) (*n* = 2)	Meerschaut et al. (2019) (*n* = 4)	Yu et al. (2019) (*n* = 6)	Alagia et al. (2018) (*n* = 1)	Garavelli et al. (2016) (*n* = 1)	Lin et al. (2016) (*n* = 3)	Bassett et al. (2016) (*n* = 1)	Starr et al. (2015) (*n* = 5)	Michot et al. (2014) (*n* = 28)	Our cohort (*n* = 10)	Total
VSD			1				1			1	2	10
ASD									1		1	4
AS										4		4
PS				1			1					5
APV												2
MS												11
MI	1											1
CA		1	2	1		1	1		1	4		19
PAS	1											4
ToF			1		1							7

Abbreviations: APV, absent pulmonary valve; AS, aortic stenosis; ASD, atrial septal defect; CA, coarctation of aorta; MI, mitral insufficiency; MS, mitral stenosis; PAS, pulmonary artery stenosis; PDA, patent ductus arteriosus; PS, pulmonic stenosis; ToF, tetralogy of fallot; VSD, ventricular septal defect.

(6/15, 40%). There was no evidence of congenital pericardial involvement. Details of the congenital cardiovascular anomalies are provided in Table 1.

3.2.2 | Musculoskeletal System

Congenital musculoskeletal abnormalities were observed in 64% (125/195) of patients. Brachydactyly was the most common anomaly, which was present in half of the whole cohort and in 78.4% (98/125) of those who had musculoskeletal anomalies. Interestingly, 13.8% (27/195) of patients had 11 pairs of ribs, and seven patients had vertebral abnormalities such as fusion of vertebrae and butterfly vertebrae. Vertebral fusion was seen in the cervical (C2–C3, C6–C7, C1–occipital bone) and thoracic (T4–T5) regions. Muscular build, which is a frequent finding in Myhre syndrome, was not reported in any of the patients within the first year of life. Limitation of joint movements or contractures at birth or within the first year of life was only observed in two patients.

Table 2 shows the congenital musculoskeletal anomalies in this cohort.

3.2.3 | Other Systems

In the whole cohort, early anomalies of the respiratory system were reported only in three (1.5%; 3/195) patients. Two of them had airway stenosis, and one had left bronchus isomerism.

Though rare, oropharyngeal anomalies can occur in Myhre syndrome. Altogether, three (1.5%; 3/195) patients in the whole cohort reportedly had cleft lip/palate.

In our analysis, we found congenital gastrointestinal anomalies in four patients. Two of them had malrotation of the small intestine, and one had concomitant duodenal stenosis. One patient had duodenal atresia, and one patient in our cohort had abnormal laterality of organs in the abdomen with duodenal obstruction. The latter was detected antenatally and confirmed postnatally. This child's antenatal ultrasound scan showed a large stomach on the right side of the abdomen with features of intermittent outflow obstruction. She had a laparotomy postnatally for the duodenal obstruction, which confirmed an annular pancreas, a transverse liver, and a right-sided stomach. She was managed as asplenic since the spleen could not be visualized.

Undescended testis was reported in five (2.6%; 5/195) patients, and one patient had small kidneys, which was detected just after birth.

Congenital anomalies of the neurological system were seen in five (2.6%; 5/195) patients. These included dilatation of ventricles and dysgenesis of the corpus callosum in three patients. Interestingly, one patient had congenital unilateral facial nerve palsy.

Inner ear anomalies were reported in 10 (5.1%; 10/195) patients, and congenital cataract and stiff skin in one (0.5%; 1/195) patient each.

TABLE 2 | Congenital anomalies of the musculoskeletal system.

	Lin et al. (2024) (*n* = 47)	Vanbelleghem (2024) (*n* = 23)	Jury et al. (2024) (*n* = 2)	Hui et al. (2023) (*n* = 3)	Brunet-Garcia (2023) (*n* = 2)	Bhushan et al. (2023) (*n* = 1)	Yang et al. (2022) (*n* = 12)	Cappuccio et al. (2022) (*n* = 6)	Yang et al. (2022) (*n* = 1)	Kilci et al. (2022) (*n* = 1)	Cătană et al. (2022) (*n* = 1)	Di Cesare (2021) (*n* = 1)	Jeon et al. (2021) (*n* = 1)	Wu et al. (2021) (*n* = 1)	Li et al. (2020) (*n* = 2)	Varenyiova et al. (2020) (*n* = 1)
Number of patients with a musculoskeletal anomaly	33	17	1	1	1	1	11	1	1	1	1	1	1	1	1	1
Clinodactyly	33		1	1	1	1	4			1	1					1
Brachydactyly	30	17	1	1			11			1	1	1	1	1		
Small hands	8						8									1
Small hands and feet								1								
Camptodactyly							2				1					
Brachycampto-dactyly																
Syndactyly of toes 2nd–3rd	31					1	2									
Syndactyly of fingers									1[a]						1[a]	
Hyperconvex nails																
Joint contractures													1			
scoliosis																
11 ribs	23															
11 vertebrae																
Polydactyly				1[b]		1[b]									1[b]	
Overlapping toes	8							1								
Brachymetar-carpia																
Fusion of vertebrae		2										1				
Butterfly vertebrae																

(Continues)

TABLE 2 | (Continued)

	Lin et al. (2024) (*n* = 47)	Vanbelleghem (2024) (*n* = 23)	Jury et al. (2024) (*n* = 2)	Hui et al. (2023) (*n* = 3)	Brunet-Garcia (2023) (*n* = 2)	Bhushan et al. (2023) (*n* = 1)	Yang et al. (2022) (*n* = 12)	Cappuccio et al. (2022) (*n* = 6)	Yang et al. (2022) (*n* = 1)	Kilci et al. (2022) (*n* = 1)	Cătană et al. (2022) (*n* = 1)	Di Cesare (2021) (*n* = 1)	Jeon et al. (2021) (*n* = 1)	Wu et al. (2021) (*n* = 1)	Li et al. (2020) (*n* = 2)	Varenyiova et al. (2020) (*n* = 1)
Hypoplasia of distal phalanges												1				
Hypoplastic proximal ulnar													1			
Hypoplastic maxilla and mandible													1			
Subluxation of the radial head													1			
Scoliosis																
Torticollis																

	Yu et al. (2019) (*n* = 6)	Meerschaut et al. (2019) (*n* = 4)	Gürsoy et al. (2020) (*n* = 1)	Artemios et al. (2019) (*n* = 1)	Erdem et al. (2018) (*n* = 1)	Alagia et al. (2018) (*n* = 1)	Nomura et al. (2017) (*n* = 1)	Lin et al. (2016) (*n* = 2)	Bassett et al. (2016) (*n* = 1)	Starr et al. (2015) (*n* = 5)	Garavelli et al. (2016) (*n* = 1)	Michot et al. (2014) (*n* = 28)	Caputo et al. (2012) (*n* = 8)	Asakura et al. (2012) (*n* = 1)	Al Ageeli et al. (2012) (*n* = 1)	Our cohort (*n* = 10)	Total
Number of patients with a musculoskeletal anomaly	5	2	1	1	1	1	1	2	1	2	1	16	8	1	1	7	125
Clinodactyly	2	2	1		1				1		1				1	3	56
Brachydactyly	4		1	1	1	1	1	1		1	1	16		1		4	98
Small hands																2	19
Small hands and feet																	1
Camptodactyly	1																4
Brachycampto-dactyly													8				8
Syndactyly of toes 2nd–3rd	1														1	2	38
Syndactyly of fingers																	2

(Continues)

TABLE 2 | (Continued)

	Yu et al. (2019) (*n* = 6)	Meer-schaut et al. (2019) (*n* = 4)	Gürsoy et al. (2020) (*n* = 1)	Artemios et al. (2019) (*n* = 1)	Erdem et al. (2018) (*n* = 1)	Alagia et al. (2018) (*n* = 1)	Nomura et al. (2017) (*n* = 1)	Lin et al. (2016) (*n* = 2)	Bassett et al. (2016) (*n* = 1)	Starr et al. (2015) (*n* = 5)	Garavelli et al. (2016) (*n* = 1)	Michot et al. (2014) (*n* = 28)	Caputo et al. (2012) (*n* = 8)	Asakura et al. (2012) (*n* = 1)	Al Ageeli et al. (2012) (*n* = 1)	Our cohort (*n* = 10)	Total
Hyperconvex nails											1						1
Joint contractures	1																2
scoliosis	1																1
11 ribs								1		2						1	27
11 vertebrae																1	1
Polydactyly																	3
Overlapping toes									1							2	12
Brachymetar-carpia							1			2							3
Fusion of vertebrae							1			1							5
Butterfly vertebrae		1														1	2
Hypoplasia of distal phalanges																	1
Hypoplastic proximal ulnar																	1
Hypoplastic maxilla and mandible																	1
Subluxation of the radial head																	1
Scoliosis		1															1
Torticollis																1	1

[a]Third and fourth fingers (Yang et al. (2022)) and first and second fingers (Li et al. 2020).
[b]Preaxial.

TABLE 3 | Congenital anomalies of other systems with their genotype.

System	Ile500Val	Ile500Thr	Ile500Leu	Arg496Cys	Total number
Respiratory					3
• Choanal atresia Inoue et al. (2021) ($n=1$)	1				
• Multilevel air way stenosis Jeon et al. (2021) ($n=1$)		1			
• Left bronchus isomerism Our cohort ($n=10$)				1	
Oropharyngeal					3
• Cleft lip and palate Lin et al. (2024) ($n=47$)	1				
• Cleft lip and palate, Cleft lip Tayara et al. (2024) ($n=2$)	1	1			
Gastrointestinal					4
• Malrotation of the small intestine Lin et al. (2024) ($n=47$)		1			
• Duodenal stenosis and malrotation Cappuccio et al. (2022) ($n=6$)	1				
• Duodenal atresia Starr et al. (2015) ($n=5$)		1			
• Duodenal obstruction and abnormal laterality of organs Our cohort ($n=10$)				1	
Genitourinary					6
• Undescended testis Lin et al. (2024) ($n=47$)					1[a]
• Undescended testis Spineli- Spineli-Silva et al. (2025) ($n=7$)	1				
• Undescended testis Yang et al. (2023) ($n=1$)	1				
• Undescended testis, Small kidneys Yu et al. (2019) ($n=6$)	1	1			
• Undescended testis Our cohort ($n=10$)				1	
Neurological					5
• Mild bilateral ventriculomegaly and mild dysgenesis of the corpus callosum Burnet- Brunet-Garcia et al. (2023) ($n=2$)	1				
• Mildly dilated ventricles, bilateral small and dysplastic lateral semicircular canals Yu et al. (2019) ($n=6$)		1			
• Periventricular leukomalacia Starr et al. (2015) ($n=5$)		1			

(Continues)

TABLE 3 | (Continued)

System	Ile500Val	Ile500Thr	Ile500Leu	Arg496Cys	Total number
• Corpus callosum agenesis with rostrum hypoplasia, mild ventriculomegaly with square-shaped lateral ventricles, and periventricular frontal increased white matter signal bilaterally Garavelli et al. (2016) ($n=1$)		1			
• Congenital unilateral facial nerve palsy Our cohort ($n=10$)		1			
Ears					10
• Inner ear anomalies Lin et al. (2024) ($n=47$)	3	3	1	2	
• Inner ear anomalies Our cohort ($n=10$)	1				
Eyes					1
• Congenital cataract Al Ageeli et al. (2012) ($n=1$)		1			
Skin					1
• Stiff skin Inoue et al. (2021) ($n=1$)	1				

[a]Genetic variant was not specified in this patient.

Table 3 shows data on congenital anomalies seen in these systems with their genotype.

3.2.4 | Anomalies Detected in Utero

Our analysis revealed that intrauterine anomalies were reported in a considerable proportion (27.7%; 54/195) of patients in this cohort. The commonest abnormality reported was intrauterine growth restriction (IUGR) (26.2%; 51/195). Oligohydramnios was seen in around 6 (3.1%; 6/195) of patients, and polyhydramnios was seen in two (1%; 2/195) patients. A few had evidence of gastrointestinal obstruction and short bones on scans. Table 4 contains details of the abnormalities reported in the intrauterine period.

3.2.5 | Genotype–Phenotype Correlation

Figure 1 illustrates the genotype–phenotype correlation studied.

Congenital cardiovascular anomalies were observed in 66.7% of cases with the c.1499T>C (p.Ile500Thr) variant, followed by 45.9% of cases with the c.1498 A>G (p.Ile500Val) variant. Congenital cardiovascular involvement was reported in 11% of cases with the c.1486 C > T (p.Arg496Cys) variant and it was not reported in patients with the c.1498 A > C (Ile500Leu) variant.

The highest percentage of congenital anomalies of the musculoskeletal system was associated with the c.1498A>G (p.Ile500Val) variant, followed by the c.1499T>C (p.Ile500Thr) variant. A predilection to developing inner ear anomalies was seen with the c.1498 A>C (p.Ile500Leu) variant. The variant c.1499T>C (p.Ile500Thr) seems to have a more severe disease phenotype considering its early-onset multisystem involvement.

4 | Discussion

SMAD4 affects signaling pathways including transforming growth factor beta (TGF-β), bone morphogenetic protein (BMP), and activin. Gain-of-function variants in this gene lead to increased TGF-β signaling, which is described as the main disease mechanism for Myhre syndrome in some studies (Lindsay et al. 2025). The presumed exaggeration of cellular responses due to increased TGF-β signaling leads to an increased sensitivity to fibrotic and calcific cellular signaling, which explains the pathophysiology behind the fibroproliferative response in Myhre syndrome (Starr et al. 2022). This is the mechanism behind some of the congenital anomalies such as airway stenosis, intestinal stenosis, and stiff skin. Other research has suggested that a dominant-negative mechanism causing an interruption of typical TGF-β and BMP signaling causes disease (Alankarage et al. 2022). Ubiquitous expression of SMAD4 is described throughout embryonic development, with high levels particularly being detected in the epithelial crypts of the intestine (Attisano and Lee-Hoeflich 2001). This might be the basis of multisystem involvement seen in Myhre syndrome. Further, there is evidence that the normal function of the SMAD4 protein is necessary for the development of cardiac and skeletal

TABLE 4 | Intrauterine anomalies with their genotype.

Anomaly	Ile500Val	Ile500Thr	Ile500Leu	Arg496Cys	Total
IUGR					51
1. Vanbelleghem et al. (2024) ($n=23$)	2	2	2	1	7
2. Jury et al. (2024) ($n=2$)	1				1
3. Bhushan et al. (2023) ($n=1$)	1				1
4. Yang et al. (2022) ($n=12$)	9	2		1	12
5. Cătană et al. (2022) ($n=1$)	1				1
6. Cappuccio et al. (2022) ($n=6$)	1				1
7. Kilci et al. (2022) ($n=1$)	1				1
8. Jeon et al. (2021) ($n=1$)		1			1
9. Yu et al. (2019) ($n=6$)		1			1
10. Alagia et al. (2018) ($n=1$)		1			1
11. Bassett et al. (2016) ($n=1$)	1				1
12. Michot et al. (2014) ($n=28$)	18				18
13. Picco et al. (2013) ($n=1$)		1			1
14. Our cohort ($n=10$)	3			1	4
Increased nuchal thickness					3
1. Jury et al. (2024) ($n=2$)				1	1
2. Cappuccio et al. (2022) ($n=6$)	1				1
3. Hui et al. (2023) ($n=1$)		1			1
Short long bones					2
1. Jury et al. (2024) ($n=2$)	1				
2. Hui et al. (2023) ($n=1$)		1			
Brachydactyly					1
1. Hui et al. (2023) ($n=1$)		1			
Abnormal curvature of the spine					1
1. Our cohort ($n=10$)		1			
Mild bilateral ventriculomegaly and mild dysgenesis of the corpus callosum					1
1. Brunet-Garcia et al. (2023) ($n=2$)	1				
Crossed fused renal ectopia					1
1. Jury et al. (2024) ($n=2$)	1				
Hyperechogenic bowel, situs inversus abdominalis, intermittent gastric outflow obstruction					1
1. Our cohort ($n=10$)				1	

Note: Oligohydramnios was seen in seven (3.6%; 6/195) patients, and polyhydramnios was seen in one (0.5%; 2/195) patient. These were not included in the above table since they are not structural anomalies.
Abbreviation: IUGR, intrauterine growth restriction.

muscles in animal models, which may explain the frequent congenital involvement of these systems in Myhre syndrome (Yang et al. 2016). The spectrum of congenital anomalies described in this paper provides evidence of the widespread effects of gain-of-function variants in *SMAD4*. The variants implicated in Myhre syndrome are in the highly conserved Mad Homology 2 (MH2) domain of the protein, hence its intolerance to missense variation (Qin et al. 1999). Loss-of-function variants in this domain lead to juvenile polyposis syndrome (Cao et al. 2023).

Our comprehensive review of the literature and search of current international databases such as DECIPHER and the 100,000

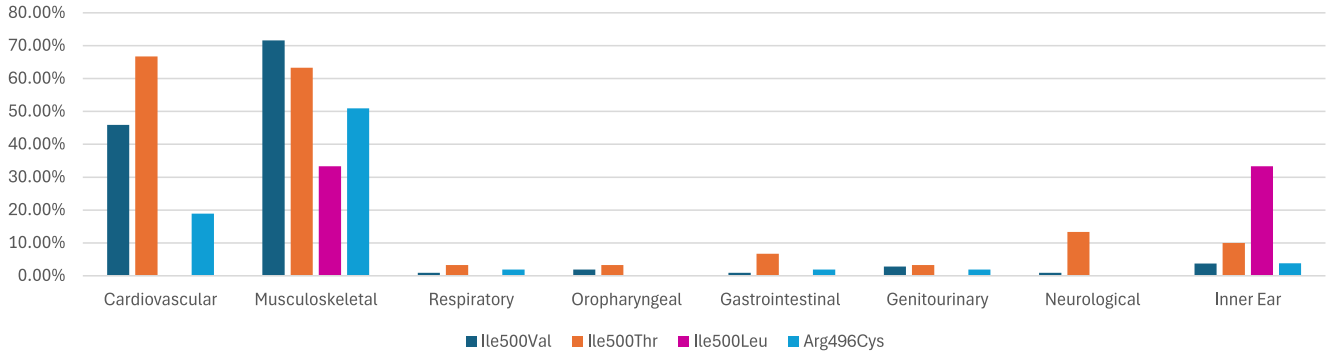

FIGURE 1 | Genotype-phenotype correlation of congenital anomalies. X axis—Organ systems, Y axis—Percentage of patients affected within each genotype.

genomes data did not reveal any new additional variants in *SMAD4* that may cause Myhre Syndrome. Ile500Val was the most common variant affecting more than half of the patients (56%) but its main effects were on the cardiovascular and musculoskeletal systems. Ile500Thr, on the other hand, had a more global effect involving multiple systems, reflecting the ubiquitous expression of *SMAD4* during embryogenesis. Additionally, serious life-threatening anomalies such as multilevel airway stenosis and unusual anomalies such as congenital facial nerve palsy and duodenal atresia were described with the latter. The exact reason for these differences in phenotype is unclear. Ile500Leu variant was reported only in three patients, and though Ile500Met was reported in literature, no patients in our cohort had this variant (Le Goff et al. 2011).

The musculoskeletal system was the most affected system across all genotypes, with brachydactyly being the most commonly reported abnormality. These anomalies are predominantly benign with no serious health implications but do have the potential to be a useful diagnostic clue when seen in combination with other anomalies such as IUGR, cardiac defects (particularly aortic involvement), airway and/or gastrointestinal stenoses. Among gastrointestinal anomalies, the duodenum appears to be the most susceptible organ across all genotypes.

The findings of our study indicate that a diagnosis of Myhre syndrome can be suspected clinically in utero or in the early neonatal period based on the concomitant occurrence of congenital anomalies, such as severe IUGR, oligohydramnios, gastrointestinal anomalies (such as bowel stenosis), cardiac anomalies and skeletal findings (for example, brachydactyly). These features, however, are not strongly specific for Myhre syndrome; rare or atypical congenital anomalies (such as multilevel airway stenosis) may, however, be a stronger indicator of the diagnosis. A gene agnostic next generation sequencing test, such as whole genome or exome sequencing, should therefore be considered. Such broad testing strategies will help to rule out other rare disorders such as Weill-Marchesani Syndrome, Geleophysic Dysplasia, Acromicric Dysplasia, Stiff Skin Syndrome and MULIBREY nanism which have overlapping features with Myhre Syndrome.

It is well-known that patients with Myhre syndrome can develop progressive multisystemic involvement, which can lead to severe morbidity and mortality later in life. Rarely, it can be fatal early in life, even in the neonatal period. Therefore, early identification is important for prognostication and effective management.

Current genetic testing technology allows the molecular confirmation of a suspected clinical diagnosis of Myhre Syndrome in utero. The early detection allows advanced planning to manage potential medical problems in the neonatal period. Additionally, prenatal diagnosis enables couples to make decisions about continuation of the pregnancy. In the current era of therapeutics, this study highlights the need for trialing intrauterine treatment given the wide range of early onset congenital anomalies in Myhre syndrome.

We acknowledge that there are limitations to our study. Most of the articles in the literature did not focus specifically on congenital anomalies, and hence, a reporting bias is to be expected. It is therefore likely that minor congenital anomalies which did not affect morbidity or mortality were under-reported. It is also possible that some congenital anomalies of the musculoskeletal and nervous systems were missed, as there was no evidence that radiological imaging had been considered. Though inner ear anomalies were reported in 10 patients, findings of the newborn hearing test could not be found, which would have been valuable additional information about the early phenotype. Future prospective studies with methodical data collection are needed to know and understand the exact spectrum of anomalies seen in Myhre Syndrome.

In summary, Myhre syndrome is a multisystemic genetic disorder caused by four recurrent gain-of-function variants in the MH2 domain of the *SMAD4* gene and characterized by multiple congenital anomalies associated with significant morbidity. Although there is no strong genotype–phenotype correlation, it appears that patients with Ile500Thr may present with involvement of multiple systems and rare and atypical anomalies. Advances in next-generation sequencing technologies are enabling early diagnosis, allowing healthcare professionals to offer appropriate management options early. The treatment options are currently limited to management of symptoms, which for many congenital anomalies is surgical intervention, which in itself has the potential to precipitate the onset of fibrosis. Emerging new molecular therapies are focused on cure rather than symptomatic management, and an early diagnosis in these patients may allow early molecular therapies in the future.

Author Contributions

Kawmadi Gunawardena: data collection, analysis, writing and editing. **Alessandro De Falco:** data collection, analysis, writing and editing cardiovascular anomalies. **Deborah Osio:** provision of clinical data. **Eleanor Sherlock:** provision of clinical data. **Emma Kivuva:** provision of clinical data. **Erina Sasaki:** provision of clinical data. **Francis H. Sansbury:** provision of clinical data. **Nayana Lahiri:** provision of clinical data. **Patricia Foley:** provision of clinical data. **Sahar Mansour:** provision of clinical data. **Shane McKee:** provision of clinical data. **Tazeen Ashraf:** provision of clinical data. **Nicola Brunetti-Pierri:** analysis and editing cardiovascular anomalies. **Usha Kini:** conceptualization, methodology, reviewing.

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The authors have nothing to report.

Ethics Statement

This study is an observational study carried out by collecting data that was gathered for clinical purposes. No specific ethical approval was therefore requested.

Consent

All genetic testing was carried out in local healthcare services using local standard consenting procedures. Consent for publication was sought for previously unreported cases from their parent or guardians.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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