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GENOTYPE: PHENOTYPE REPORT

PRENATAL DIAGNOSIS WILEY

Prenatal diagnosis of Myhre syndrome with a heterozygous pathogenic variant in *SMAD4* gene presented with thick nuchal translucency and cardiac abnormalities

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Abstract

Prenatal testing was performed in a 39-year-old Chinese pregnant woman referred for increased nuchal translucency measuring 5.7 mm. Non-invasive prenatal testing and SNP array study on amniotic fluid samples were normal. Whole exome sequencing (WES) was initiated further as the fetus had pericardial effusion of 1.2 mm, thickened myocardium over the right ventricular lateral wall and aberrant right subclavian artery. A detailed fetal echocardiogram also revealed persistent left superior vena cava and dilated coronary sinus at 20 weeks. From whole exome sequencing of the trio, a de novo heterozygous variant NM_005359.5(*SMAD4*): c.1499T>C (p.Ile500Thr) was detected. This pathogenic variant has been reported in the postnatal case cohort of Myhre syndrome. This condition is characterized by facial dysmorphism, intellectual disability, hearing loss, skeletal abnormalities and potential life threatening respiratory or cardiovascular manifestations. Termination of pregnancy was performed at 23 weeks. Small chins, pre-axial polydactyly, brachydactyly and clinodactyly were noted in the abortus. Ultrasound findings of increased nuchal translucency, thickened myocardium and pericardial effusion prompted further genetic evaluation for the prenatal diagnosis of Myhre syndrome by whole exome sequencing.

Key points

What is already known about this topic?

- Myhre syndrome is a rare condition reported only once prenatally.
- Very limited information on the prenatal manifestations is available.

What does this study add?

- Fetus with Myhre syndrome can present with increased nuchal translucency, thick myocardium and pericardial effusion.

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- Brachydactyly can be detected sonographically.
- Prenatal whole exome sequencing identified a de novo heterozygous pathogenic variant in the *SMAD4* gene in fetus with thick nuchal translucency and features of cardiomyopathy, allowing prenatal diagnosis of Myhre syndrome.

1 | FETAL PHENOTYPE

A 39-year-old pregnant woman attended for prenatal diagnosis because of increased nuchal translucency measuring 5.7 mm at 11 weeks and 2 days of gestation. This was a Chinese couple with no family history of hereditary or congenital abnormality. They had a normal healthy girl delivered 8 years ago. The present pregnancy was conceived by in vitro fertilisation. Ultrasound at 19 weeks 3 days showed mild pericardial effusion of 1.2 mm, thickened myocardium over the right ventricular lateral wall and aberrant right subclavian artery (Figure 1). Bilateral kidneys looked echogenic. Repeated fetal echocardiography revealed persistent left superior vena cava and dilated coronary sinus at 20 weeks (Table 1). A follow-up scan at 22 weeks showed short

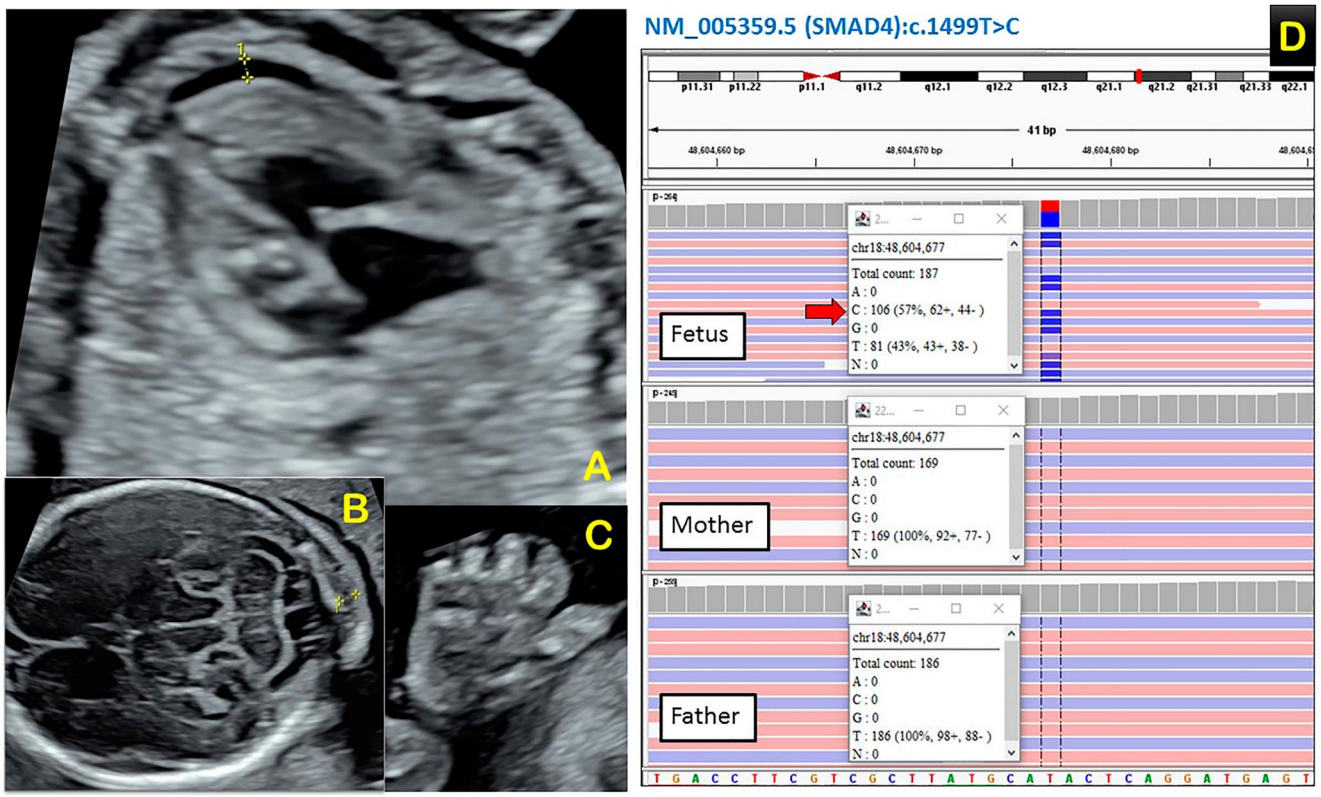

FIGURE 1 Prenatal ultrasound at 19 weeks of gestation showing thickened pericardium and pericardial effusion (1.2 mm) reflecting possible underlying cardiomyopathy (A). There was persistently increased nuchal fold and bradydactyly (B&C). Integrative genomics viewer demonstrating a de novo heterozygous variant NM_005359.5(SMAD4): c.1499T>C (p.Ile500Thr) detected by Whole exome sequencing (WES) representing Myhre syndrome (D).

TABLE 1 Clinical data.

Case	Parental details			Gestation at diagnosis	Phenotypes (HPO terms)	Obstetric history	Family history	Outcome
1	Maternal	Age	39	23 weeks	HP:0010880 increased nuchal translucency HP:0001698 pericardial effusion HP:0031014 aberrant right subclavian artery HP:0005301 persistent left superior vena cava	G2P1 Normal full term delivery of a baby girl at age of 30	Unremarkable	Pregnancy termination
		ethnicity	Chinese					
	Paternal	Age	41					
		ethnicity	Chinese					

long bones, but the kidneys were then considered normal in echogenicity with cortico-medullary differentiation seen. Brachydactyly was also noted upon retrospective review of the stored ultrasound images.

2 | DIAGNOSTIC METHOD

The patient had noninvasive prenatal testing done prior to the referral, and the result was negative for common aneuploidies and sex chromosomes in a male fetus. Amniocentesis was performed for 17 weeks' gestation, which was complicated by leaking which gradually sealed off with no signs of intrauterine infection. Chromosomal microarray analysis found no copy number gains or losses greater than 100Kb across the genome using an Affymetrix CytoScan 750k SNP array. Trio exome sequencing analysis of the DNA of the uncultured amniotic fluid sample and parental blood was performed at 20 weeks' gestation and the result was available at 22 weeks of gestation.

3 | DIAGNOSTIC RESULTS AND INTERPRETATION

From whole exome sequencing, a heterozygous c.1499T>C (p.Ile500Thr) variant in exon 12 of SMAD family member 4 (*SMAD4*) gene was detected in the fetus (Figure 1). Heterozygous pathogenic variants of the *SMAD4* gene were associated with autosomal dominant Myhre syndrome (OMIM 139210), juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (OMIM 175050) and polyposis, juvenile intestinal (OMIM 174900). The c.1499T>C (p.Ile500Thr) missense variant was predicted to change the amino acid at position 500 in the MH2 domain from isoleucine to threonine. Multiple lines of computational evidence predicted a deleterious effect of the variant on the gene. The variant was absent in controls in the Genome Aggregation Database (GnomAD). The variant had been reported as pathogenic for Myhre syndrome in ClinVar (Variation ID: 30149). The variant was not found in the parents, suggesting its de novo occurrence in the fetus (Table 2). The variant was considered pathogenic according to the American College of Medical Genetics and Genomics guidelines.

4 | PREGNANCY OUTCOMES AND NEONATAL FINDINGS

The genetic finding was consistent with the diagnosis of Myhre syndrome. The recurrence risk in future pregnancy is about 1% because of the possibility of parental germline mosaicism. The patient decided to have a termination of pregnancy after knowing the WES result at 23 weeks. Small chins, pre-axial polydactyly, brachydactyly and clinodactyly were noticed on gross examination. The couple declined postmortem examination.

TABLE 2 Genetic findings.

Procedure (Gest age)	Direct/culture?	Performed test	Secondary confirmatory test	Gene (name; REFSEQ)	Known disease (OMIM)	Variant	ACMG classify-cation	Criteria applied	Inheritance and zygosity	Interpret-ation
Amniocentesis 17 weeks 3 days	Direct	1.Chromosomal microarray	Nil	Nil	Nil	Nil	NA	NA	NA	NA
20 weeks 2 days		2.Whole exome sequencing	Nil	SMAD4 (NM_005359.5)	Myhre syndrome, autosomal dominant (OMIM 139210)	c.1499T>C p.Ile500Thr	Pathogenic	PS2, PM1, PM2_Supporting, PM5, PP2, PP3	De novo, heterozygous	Consistent with autosomal dominant Myhre syndrome

5 | DISCUSSION

Myhre syndrome is a rare multi-system disorder due to mutations in the *SMAD4* gene. Heterozygous *SMAD4* c.1499T>C (p.Ile500Thr) is a known gain-of-function mutation, which was demonstrated to increase *SMAD4* stability and impaired *transforming growth factor beta* (TGF-beta) mediated transcriptional control in fibroblasts isolated from Myhre syndrome patients. Such a gain-of-function mutation is in contrast to other *SMAD4* loss-of-function variants, preferably through preventing homo-and/or-hetero-oligomerization with other SMAD proteins, and is associated with a loss of tumor suppressive roles in carcinogenesis.[1–3] Most patients have intellectual disability and growth abnormalities. Hearing loss, visual problem, midface hypoplasia and thick skin could present in more than half of the patients.[4] The presence of restrictive cardiomyopathy and pericardial phenotypes distinguish Myhre syndrome from other disorders caused by mutations in the TGF-b signaling cascade.[5] Clinical diagnosis could be challenging even postnatally as affected individuals might have variable presentations which progressively manifested in later life, and only one case was reported prenatally that presented as facial dysmorphism and abnormal corpus callosum.[6] The in-utero findings of thickened myocardium and pericardial effusion in the present case could represent a fetal manifestation of restrictive cardiomyopathy in postnatal life, and these in-utero features were not reported in literature before. In addition, the presence of polydactyly could also present a new clinical phenotype. A detailed ultrasound evaluation would allow the detection of brachydactyly. Together with the presentation of increased nuchal translucency, these cardiac features prompted further genetic evaluation for this second case of prenatally diagnosed Myhre syndrome.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL AND PUBLICATION CONSENT

Consent has been obtained from the pregnant woman for this publication.

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