Received: 4 May 2020 | Revised: 25 May 2020 | Accepted: 1 June 2020

DOI: 10.1002/mgg3.1377

CLINICAL REPORT

Molecular Genetics & Genomic Medicine Open Access WILEY

Expanding the phenotype of *STRA6*-related disorder to include left ventricular non-compaction

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Funding information

National Key R&D Program of China, Grant/Award Number: 2018YFC1002300; Beijing Laboratory for Cardiovascular Precision Medicine, Beijing, China (116211), Grant/Award Number: PXM2017_014226_000037

Abstract

Background: Syndromic microphthalmia-9 (MCOPS9) is a rare autosomal recessive disorder caused by mutations in *STRA6*, an important regulator of vitamin A and retinoic acid metabolism. This disorder is characterized by bilateral clinical anophthalmia, pulmonary hypoplasia/aplasia, cardiac malformations, and diaphragmatic defects. The clinical characteristics of this disorder have not been fully determined because of the rarity of clinical reports.

Methods: A comprehensive genotyping examination including copy number variation sequencing (CNV-Seq) and whole-exome sequencing (WES) was applied to a fetus of Han Chinese with bilateral anophthalmia, bilateral pulmonary agenesis, interrupted aortic arch type A, and left ventricular non-compaction (LVNC).

Results: No aneuploidy or pathogenic CNV were identified by CNV-seq. WES analysis revealed a previously reported homozygous splice site (NM_022369.4:c.113+3_113+4del) in the *STRA6* gene. This variant was confirmed by Sanger sequencing. The diagnosis of MCOPS9 was confirmed given the identification of the *STRA6* mutation and the association of bilateral anophthalmia, pulmonary agenesis, and cardiac malformations.

Conclusion: This case adds to the phenotypic spectrum of MCOPS9, supporting the association with LVNC, and the presence of interruption of aortic arch further demonstrates the variability of the cardiac malformations.

KEYWORDS

anophthalmia/microphthalmia, left ventricular non-compaction, Matthew-Wood syndrome, *STRA6*, syndromic microphthalmia-9

1 | INTRODUCTION

Syndromic microphthalmia-9 (MCOPS9; OMIM 601186), also referred to as Matthew-Wood syndrome or pulmonary hypoplasia-diaphragmatic hernia-anophthalmia-cardiac defect, is characterized by bilateral clinical anophthalmia, pulmonary hypoplasia/aplasia, cardiac malformations, and diaphragmatic defects (Marcadier et al., 2016). MCOPS9

Hairui Sun and Shaomei Yu have contributed equally to this work.

is a rare, autosomal recessive disorder caused by mutations in *STRA6* (OMIM 610745), an important regulator of vitamin A and retinoic acid (RA) metabolism (Kawaguchi et al., 2007). To date, a total of 44 patients with bi-allelic *STRA6* mutations have been described in the literature. The phenotype is variable, ranging from isolated clinical anophthalmia or microphthalmia to complex presentations involving the cardiac, pulmonary, diaphragmatic, and renal systems; congenital heart defects are seen in more than half of cases, with varying levels of severity (Marcadier et al., 2016; Pasutto, Flinter, Rauch, & Reis, 2018). However, due to the scarcity of clinical reports, the clinical characteristics of MCOPS9, especially phenotypes with variable expressivity, such as cardiovascular abnormalities, have not been fully determined.

Here, we describe a fetus of Han Chinese with bilateral anophthalmia, bilateral pulmonary agenesis, interrupted aortic arch type A, and left ventricular non-compaction (LVNC). The presence of LVNC further broadens the phenotypic spectrum of MCOPS9.

2 | ETHICAL COMPLIANCE

This study was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. Written consent for publication has been obtained.

3 | CLINICAL PHENOTYPES AND MOLECULAR FINDINGS

A 32-years-old gravida 2 para 0 pregnant woman of Han Chinese was referred to our hospital due to multiple fetal abnormalities at 22 weeks of gestation. The woman was healthy and did not take any medication. She and her

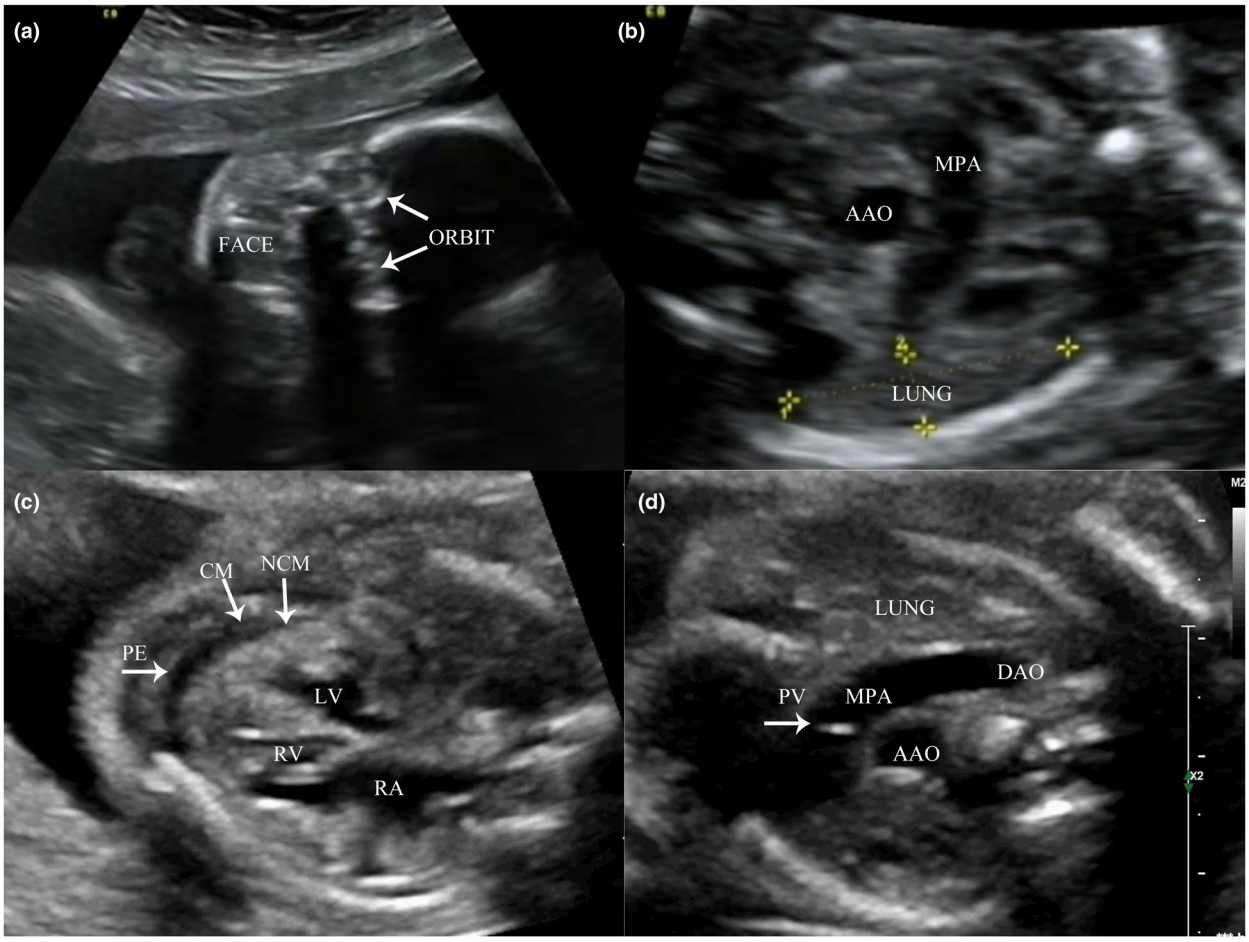

FIGURE 1 Phenotype of the fetus: Bilateral anophthalmia (a), bilateral pulmonary agenesis (b), left ventricular non-compaction (c), and interruption of aortic arch. (a) The fetal eye globes and lenses could not be seen on two-dimensional ultrasound. (b) No lung tissue was identified in the right cavity, and a small amount of lung tissue (yellow scale range) was presented in the left thoracic cavity. (c) Left ventricular non-compaction and pericardial effusion. (d) The main pulmonary artery directly extended into descending aorta, and both the left and right pulmonary arterys were absent. AAO, ascending aorta; CM, compact myocardium; DAO, descending aorta; LV, left ventricle; MPA, main pulmonary artery; NCM, Non-compact myocardium; PE, pericardial effusion; PV, pulmonary valve; RA, right atrium RV, right ventricle

partner were non-consanguineous. The family history indicated that a previous pregnancy was terminated due to multiple malformations including congenital heart disease (details are not available). The initial ultrasound examination, performed at 13 weeks of gestation reported no abnormalities.

A second ultrasound examination performed at 22 weeks of gestation revealed several malformations: bilateral anophthalmia (Figure 1a), bilateral pulmonary agenesis (Figure 1b), and fetal cardiac abnormalities. Detailed fetal cardiac evaluation revealed LVNC (Figure 1c) and interrupted aortic arch type A. The main pulmonary artery originated from the right ventricle and directly extended into descending aorta (Figure 1d), and both the pulmonary vein and the pulmonary artery were absent. Slight pericardial effusion was observed (Figure 1c). The rest of the cardiac anatomy was normal. After detailed counseling, the couple decided to terminate with the pregnancy and have genetic tests but declined to have an autopsy.

A trio (fetus and the parents) whole-exome sequencing (WES) and copy number variation sequencing were performed using methods as previously described (Sun et al., 2019). WES identified a previously reported homozygous splice site mutation in *STRA6* (NM_022369.4:c.113+3_113+4del) (Figure 2). This variant was present in the heterozygous state in both parents. It has been reported previously in homozygous in two individuals with MCOPS9 (Marcadier et al., 2016) and was not found in the biggest general population database (gnomAD, https://gnomad.broadinstitute.org). This variant showed a deleterious effect by multiple in silico algorithms. Experimental evidence shows that this variant alters splicing in vitro. In conclusion, the variant is classified as pathogenic according to the American College of Medical Genetics and Genomics guidelines (Richards et al., 2015).

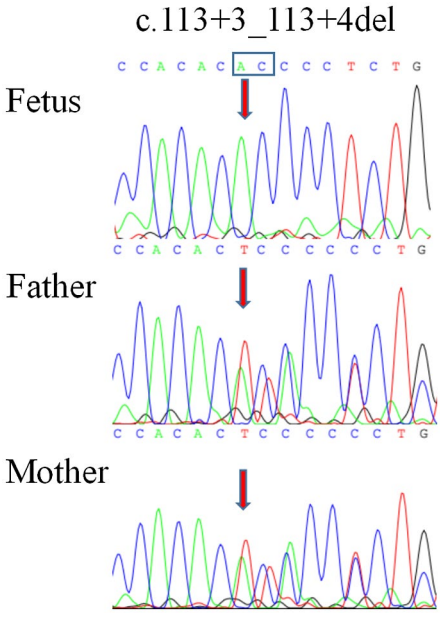

FIGURE 2 Sanger sequencing shows that the c.113+3_113+4del deletion is homozygous in the fetus heterozygous in the parents

Besides the finding of *STRA6* mutation presented above, we also analyzed variants in known LVNC or cardiomyopathy genes (Table S1). For known LVNC or cardiomyopathy genes, pathogenicity of variants was determined according to the American College of Medical Genetics and Genomics guidelines that recommend classifying variants into five categories: pathogenic, likely pathogenic, uncertain significance, likely benign, or benign (Richards et al., 2015). Variants were filtered out if their minor allele frequency among East Asians in the GnomAD database: ≥ 0.01% for variants associated with autosomal dominant disorders and ≥1% for variants associated with autosomal recessive disorders, respectively. We then evaluated each variant considering a careful review of the literature and in silico prediction tools (SIFT, Polyphen-2, and Mutation Taster for missense variants and MaxEntScan, GeneSplicer and Human Splicing Finder for splicing variants). As a result, no pathogenic/likely pathogenic variants in known LVNC or cardiomyopathy genes were identified.

4 | DISCUSSION

This report describes a fetus with bilateral anophthalmia, bilateral pulmonary agenesis, interrupted aortic arch type A, and LVNC who was found to have a splicing variant in the *STRA6* gene. This case adds to the phenotypic spectrum of MCOPS9, supports the association with LVNC.

Vitamin A metabolism plays an important role in the formation of the compact myocardial layer of the ventricular wall during cardiac development (Lin et al., 2010; Niederreither et al., 2001). Normal ventricular myocardial compaction depends on the proper amount of the active derivative of vitamin A, RA (Stefanovic & Zaffran, 2017). RA deficiency during rat embryogenesis has been reported to cause thinned and hypoplastic compact myocardial layer (Wilson & Warkany, 1949). Genetic ablation of several genes in the RA synthesis pathway can cause LVNC, despite the involvement of distinct genes (Dyson et al., 1995; Stefanovic & Zaffran, 2017; Sucov et al., 1994). Non-compaction of the ventricular myocardium has been confirmed in retinaldehyde dehydrogenase 2 (*RALDH2*) knockout mice (Lin et al., 2010); *RALDH2* is the major enzyme for RA synthesis. Mouse embryos lacking the RA receptor RXRα develop a severe growth defect of the compact myocardial layer resembling non-compaction cardiomyopathy (Dyson et al., 1995; Sucov et al., 1994). These data indicate a potentially general role for components of RA pathway in LVNC. Since *STRA6* is the major transmembrane receptor/transporter protein involved in cellular uptake of vitamin A through binding of retinol binding protein, *STRA6* deficiency can interrupt the vitamin A and RA metabolism, and may lead to LVNC. The

Novel phenotype of LVNC in this patient supports the association between *STRA6* mutations and LVNC and may help clinicians recognize this less frequent manifestation of MCOPS9.

Some phenotypic similarities to previously reported patients were observed in this fetus, namely bilateral anophthalmia, bilateral lung and pulmonary artery agenesis, and congenital heart disease (interrupted aortic arch type A). Notably, although ~50% of the previously reported patients with MCOPS9 had CHD (Marcadier et al., 2016), this fetus is the first with interrupted aortic arch, suggesting the variability of the cardiac malformations.

5 | CONCLUSION

In conclusion, we describe a further individual with *STRA6* mutation who presented with bilateral anophthalmia, bilateral pulmonary agenesis, interrupted aortic arch, and LVNC, expanding the phenotypic spectrum of MCOPS9.

ACKNOWLEDGMENTS

This work was supported by National Key R&D Program of China (2018YFC1002300), and Beijing Laboratory for Cardiovascular Precision Medicine, Beijing, China (116211), code: PXM2017_014226_000037. We thank the family for their cooperation.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Hongjia Zhang, Hairui Sun, and Yihua He designed the study. Shaomei Yu and Xiaoxue Zhou collected the clinical data and samples from the family. Hairui Sun and Lu Han analyzed and interpreted the data. Hairui Sun and Shaomei Yu wrote the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

How to cite this article: Sun H, Yu S, Zhou X, Han L, Zhang H, He Y. Expanding the phenotype of *STRA6*-related disorder to include left ventricular non-compaction. *Mol Genet Genomic Med*. 2020;8:e1377. https://doi.org/10.1002/mgg3.1377