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Clinical Report

Pathogenic variant in *GATA4* associated with atrioventricular septal defect and congenital diaphragmatic hernia: A case report

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ABSTRACT

Pathogenic variants in *GATA4*, a transcription factor, are predominantly associated with congenital heart defects and gonadal abnormalities. We describe a case of a maternally inherited *GATA4* pathogenic variant (c.474C > G p.[Tyr158Ter]) in a 21-week gestation fetus presenting with partial atrioventricular septal defect and congenital diaphragmatic hernia. Whilst there is a weight of evidence implicating GATA4 dysfunction in congenital diaphragmatic hernia, this is only the second report to our knowledge to identify a causative *GATA4* variant with congenital diaphragmatic hernia.

1. Introduction

GATA4 encodes a zinc finger transcription factor involved in regulating gene expression in various mesoderm and endoderm-based tissues (Molkentin, 2000). Its messenger RNA has been detected in embryonic gonads, liver, heart and gut (Arceci et al., 1993). It regulates expression of numerous genes associated with myocardial development (Kuo et al., 1997) and continues to be expressed in the heart in adulthood (Heikinheimo et al., 1994).

Pathogenic variants of *GATA4* are a recognised cause of congenital heart defects (Zhang et al., 2017); more than 60 cases have been identified (Arceci et al., 1993). Implicated variants have been shown to affect myocardial development by suppressing DNA transcription (Yang et al., 2012), decreasing target gene activation (Zhang et al., 2016) and altering micro-RNA (miRNA) post-transcriptional changes (Pulignani et al., 2016).

GATA4 pathogenic variants can cause a broad spectrum of congenital heart defect and severity (Fang, 2019). The most common are atrial septal defects (ASD), ventricular septal defects (VSD), Tetralogy of Fallot and transposition of the great arteries (Tomita-Mitchell et al., 2007).

Congenital diaphragmatic hernia (CDH) is an uncommon congenital malformation in which gut parenchyma herniates into the thorax due to a defect in the diaphragm (Keijzer et al., 2010). The condition is associated with pulmonary hypoplasia and respiratory distress and consequently carries a high risk of postnatal mortality and morbidity (Leeuwen et al., 2014). Its genetic associations are complex and not fully characterised (Brosens et al., 2022) – it is estimated that 3.4 % of cases are syndromic (Burgos et al., 2023).

Here we describe a case of a 21-week gestation twin fetus with a heterozygous *GATA4* stop-gain pathogenic variant (c.474C > G p.[Tyr158Ter]). The fetus presented with both partial atrioventricular septal defect and left sided CDH. We review previous evidence of *GATA4* variants association with CDH.

2. Clinical report

A 30-year-old lady, gravida 2 para 1, was pregnant with dichorionic diamniotic twins. Routine ultrasound at 21 weeks had provoked concerns of a possible CDH in one of the twins. A previous scan at 12 + 4 weeks was otherwise unremarkable, with crown rump length equivalent to gestation for both twins (61 and 62mm) and normal nuchal translucency (2.2 and 2.2mm).

No abnormalities were detected in the male twin. In the female twin, a left sided CDH containing stomach, bowel and a section of the left lobe of the liver was seen, associated with significant mediastinal shift and left-right mediastinal disproportion. The lung-to-head ratio was 47 %.

In addition, a partial atrioventricular septal defect (AVSD) and bilateral superior vena cava were seen, with the left superior vena cava

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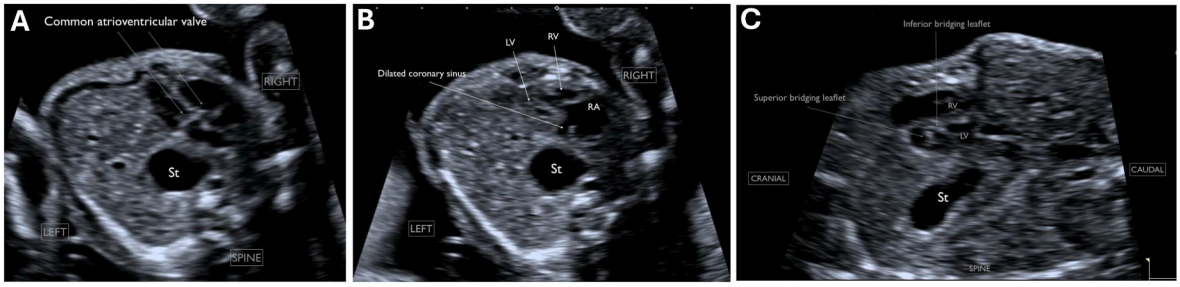

Fig. 1. Sonography of Congenital Heart Defects and Herniating Stomach Parenchyma at 21 Weeks.
A – The heart is displaced into the right hemithorax. There is ventricular asymmetry and the subtle appearance of a partial atrioventricular septal defect can be appreciated. The stomach is herniating into the thorax via the congenital diaphragmatic hernia.
B – The heart is displaced into the right hemithorax. There is ventricular asymmetry and a dilated coronary sinus can be seen. The left superior vena cava drains into this. The stomach is herniating into the thorax via the congenital diaphragmatic hernia.
C - In this sagittal view, two of the three leaflets of the left atrioventricular valve can be seen. The stomach is herniating into the thorax via the congenital diaphragmatic hernia.

draining to a dilated coronary sinus (Fig. 1). There was a degree of ventricular asymmetry, a common finding with a left-sided CDH, in the context of an apex-forming left ventricle, and a normal-sized aortic isthmus for gestation. Finally, a single (left) umbilical artery was seen. No other fetal abnormalities were evident on ultrasound. A fetal MRI at 31 weeks' gestation showed the total lung volume was 28 % of predicted.

The mother's first child, now 19 months of age, was healthy. The father reported no abnormalities. The mother reported she was born with an atrial septal defect, surgically repaired at 18 months and later diagnosed with a bicuspid aortic valve. She did not have a diaphragmatic hernia. To our knowledge, there were no other relatives on the mother's side with cardiac or diaphragmatic defects.

The twins were born by elective caesarean section at 37 weeks gestation. The affected twin's birth weight was 2290g ($z = -1.22$) and the non-affected twin's was 2820g ($z = -0.1$). The affected twin survived surgery, during which there was found to be a near complete agenesis of diaphragm apart from a 1cm rim around the oesophageal hiatus and narrow anterior rim to 1/3 of defect. The non-affected twin had a structurally normal postnatal echocardiogram but has not yet been tested for the familial variant.

3. Molecular analysis

Following the identification of the abnormalities, counselling and discussion of all the options, the mother opted for amniocentesis in the affected twin. DNA was extracted from amniocytes from the affected fetus and from blood samples from the mother and father. QFPCR and single nucleotide polymorphism (SNP) array of the fetal DNA were normal. Rapid genetic testing was performed on the fetal and parental DNA against a panel of genes understood to be associated with the fetal malformations. These were based on the Genomics England fetal abnormalities v3.0 panel. From this, a heterozygous, pathogenic stop-gain variant in *GATA4* NM_001308093.3:c.474C > G p.(Tyr158Ter) was identified. This variant causes a premature truncation of the GATA4 protein and is predicted to undergo nonsense mediated decay (PVS1_very-strong). The variant is not listed in the gnomAD population database (PM2_moderate). This variant has not been reported previously, but other loss of function variants in the same domain have been reported as causative. Therefore, this variant has been classified as class 5 Pathogenic. The variant has been added to the open-access database, DECIPHER - (NHS-GEO), ID 328336. The mother was also heterozygous for this variant.

4. Discussion

Characterising the poorly understood genetic aetiology of CDH has been a challenge (Bogenschutz et al., 2020). GATA4 dysfunction has been implicated through animal studies (Schreiner et al., 2021); in murine samples with *GATA4* mosaic mutations, connective tissue fibroblasts have been identified as the causative site of biomechanical weakness (Merrell et al., 2015).

Wat et al. (2009) described a case of monozygotic twins with *de novo* deletions of 8p23.1, the short arm of chromosome 8 and locus of *GATA4*. One twin presented with cardiac defects and a left sided CDH, the other with cardiac defects only. Mice with a heterozygous *GATA4* deletion (Jay et al., 2007) showed a similar phenotype of congenital heart defect and CDH to the case reported, supporting haploinsufficiency of *GATA4* as the underlying cause.

To our knowledge, there is only one previous report which identifies *GATA4* variants in cases of CDH (Yu et al., 2013). This was established by performing whole exome sequencing on a family from the DHREAMS (Diaphragmatic Hernia Research & Exploration; Advancing Molecular Science) study. The proband had a left sided CDH with herniating stomach, liver, spleen and bowel, diagnosed at 20 weeks. They had no structural heart defects. They had one paternal uncle who had died at day two of life from respiratory failure secondary to a left sided CDH and another who had died at day one of life, the cause was unclear. A novel stop gain variant (c.848G > A; p.[Arg283His]) with autosomal dominant inheritance was identified. MRI imaging identified structural irregularities in the diaphragms of a further two asymptomatic relatives, confirming the variant was fully penetrant.

On screening of a further 96 sporadic congenital heart defect patients, the study also identified *a de novo GATA4* (c.848G > A p.Arg283His) variant in a child with ASD, VSD, CDH and mild cognitive delay.

Alongside the two cases reported by Yu et al., the described murine embryological studies and the reported incidence of CDH in 8p23.1 deletions, our finding of a fetus presenting with AVSD and a CDH with an inherited *GATA4* pathogenic variant adds further evidence to its implication as a cause of CDH. For patients co-presenting with structural heart disease and CDH, *GATA4* variants should be considered as a potential syndromic cause.

CRediT authorship contribution statement

John Howat: Writing – original draft. **Trisha Vigneswaran:** Writing – review & editing. **Aris Papageorghiou:** Writing – review & editing. **Sahar Mansour:** Writing – review & editing.

Data availability

No data was used for the research described in the article.

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