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Chromosome 15q13.1q13.2 microdeletion in a foetus with severe congenital heart defects: A case report

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Abstract:

Congenital heart disease (CHD) is a complex condition affecting the heart's structure and function, leading to serious health problems. While the cause of CHD is not well understood, researchers have identified copy number variations (CNVs) as potential contributors to its pathogenesis. One such CNV is the rare chromosome 15q13 microdeletion, but its role in CHD remains unclear. In a 22-week gestation foetus, severe congenital heart defects were detected by colour Doppler ultrasound imaging. Array comparative genomic hybridisation (aCGH) was performed, revealing a 1.1 Mb deletion of the chromosome 15q13.1-q13.2 region containing five genes (*APBA2*, *NSMCE3*, *TJP1*, *FAM189A1*, *LOC100130111*). However, further chromosomal G-banding revealed no abnormal karyotype. Parental aCGH testing determined that this mutation was de novo. This report demonstrates the potential association between chromosome 15q13.1-q13.2 microdeletion and foetal congenital heart defects for the first time. The use of aCGH in foetuses with abnormal cardiac development diagnosed by routine cardiac colour Doppler ultrasound imaging is recommended for the early detection of congenital genetic abnormalities. This information can provide valuable insight for prenatal diagnostic consultation and decisions regarding pregnancy termination.

Keywords: **array, chromosome, comparative, congenital, defects, genomic, heart, hybridisation, microdeletion, 15q13.1-q13.2.**

Classification numbers: **3.2, 3.6**

1. Introduction

Congenital heart disease is a significant health concern as it is the primary cause of birth defects and the leading cause of infant mortality after excluding infectious aetiologies [1]. With an incidence ranging from 19 to 75 per thousand live births and present in an even greater proportion of miscarriages, CHD is a major contributor to childhood morbidity and mortality worldwide. Despite its prevalence, the cause of the majority of CHD cases remains unknown, although genetic factors are increasingly recognised as playing a significant role [2]. Furthermore, approximately 30% of children with abnormal chromosomal numbers, or aneuploidy, will develop CHD [3]. Understanding the genetic basis of CHD is crucial for developing effective prevention, diagnosis, and treatment strategies for this devastating condition.

The advancement of technology has led to the identification of submicroscopic CNVs associated with genetic disorders through the use of high-resolution microarrays in clinical analysis. Several studies have found that patients with CHD and other anomalies are highly likely to carry previously undetected CNVs, leading to the identification of new disease-related genes or loci for various cardiac defects [4, 5].

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Microdeletions, a type of CNV, can encompass multiple genes. Although they are uncommon in chromosome 15q13, their contribution to CHD remains incompletely elucidated.

In the presented case, an amniotic sample was obtained from a 22-week-old foetus exhibiting numerous congenital heart abnormalities. The sample was analysed using aCGH, which revealed a 1.1 Mb deletion on the long arm of chromosome 15 (46, XX [del (15). q13.1-q13.2]). Further investigation confirmed that this deletion occurred spontaneously. It is therefore hypothesised that this mutation is solely responsible for the observed congenital heart defects.

2. Case presentation

A 29-year-old pregnant woman (G1P0) was admitted to the hospital for evaluation at 22 weeks of gestation. Foetal echocardiography was performed using 2-dimensional, M-mode, and Doppler imaging. A colour Doppler ultrasound revealed several heart abnormalities, including dextrocardia, a significant atrioventricular

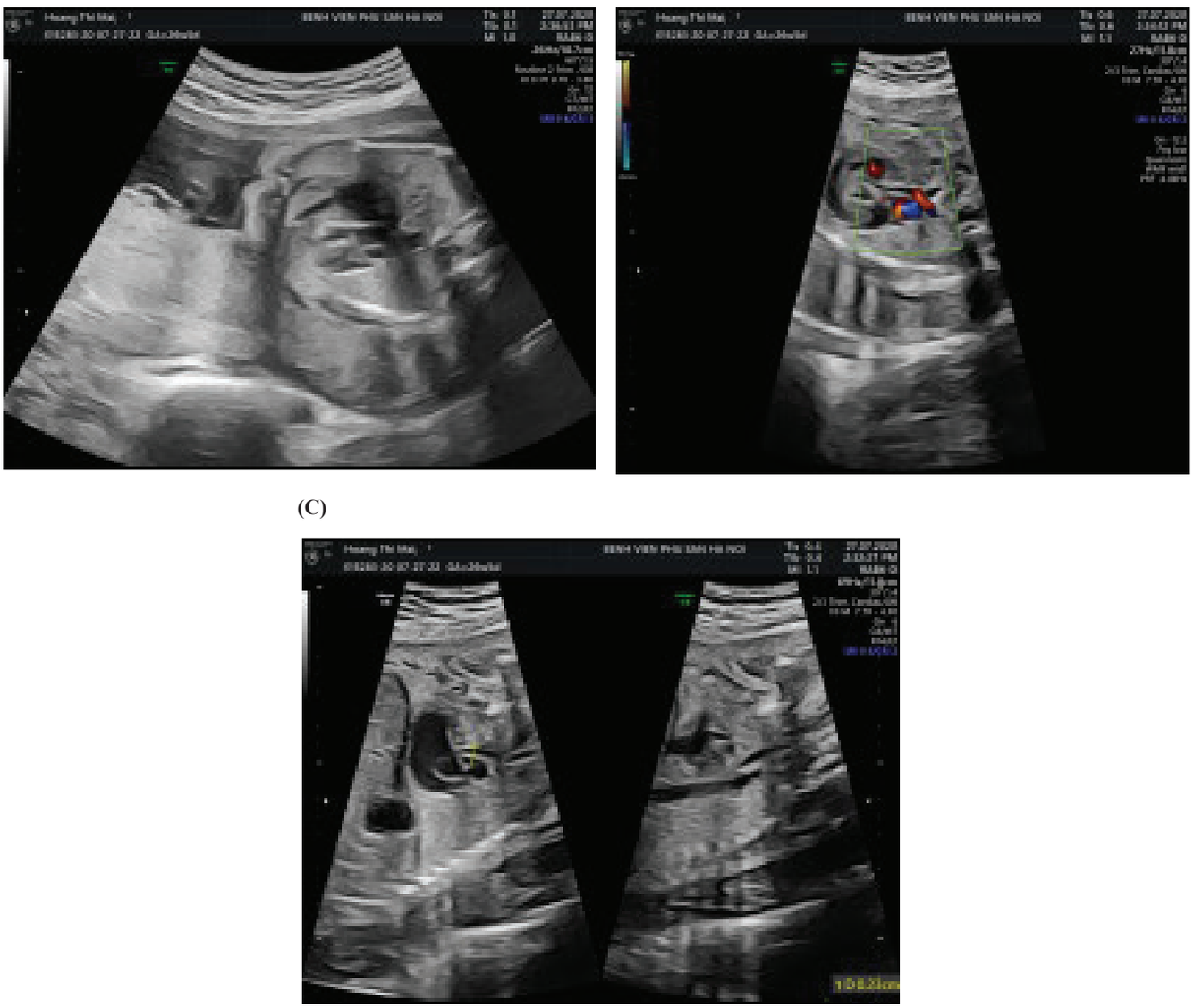

Fig. 1. Colour Doppler ultrasound imaging showing (A) dextrocardia, significant atrioventricular septal defect and (B) aortic valve stenosis, (C) pulmonary valve stenosis.

septal defect (AVSD), and stenosis of the aortic and pulmonary valves (Fig. 1). The ventricular septum was examined carefully for cardiac wall defects, from the apex to the crux. Septal defects may be difficult to detect. The septum was detected when the ultrasound section was perpendicular to it, starting from a four-chamber view to obtain the normal cross-over of the aorta and main pulmonary artery at their origin. Details of the pulmonary artery bifurcation can also be seen. Other parts of the foetus showed no abnormalities. Ultrasound was performed on a GE Volution E10 machine from a healthcare company.

Approximately 20 ml of amniotic fluid was collected using ultrasound-guided transabdominal puncture. The fluid underwent conventional chromosomal G-banding karyotype analysis and aCGH analysis with CytoGenomic version 5.0, compared with GRCh37/hg19. The G-banding analysis revealed a 46, XY karyotype with no abnormalities detected. However, the aCGH analysis identified a 1.1 Mb deletion in the chromosome 15q13.1-q13.2 region (arr[GRCh37] 15q13.1q13.2(29253317_30366124)x1) containing five genes (*APBA2, NSMCE3, TJP1, FAM189A1, LOC100130111*). This deletion occurred between BP3-BP4 on chromosome 15q13.1-q13.2 (Fig. 2).

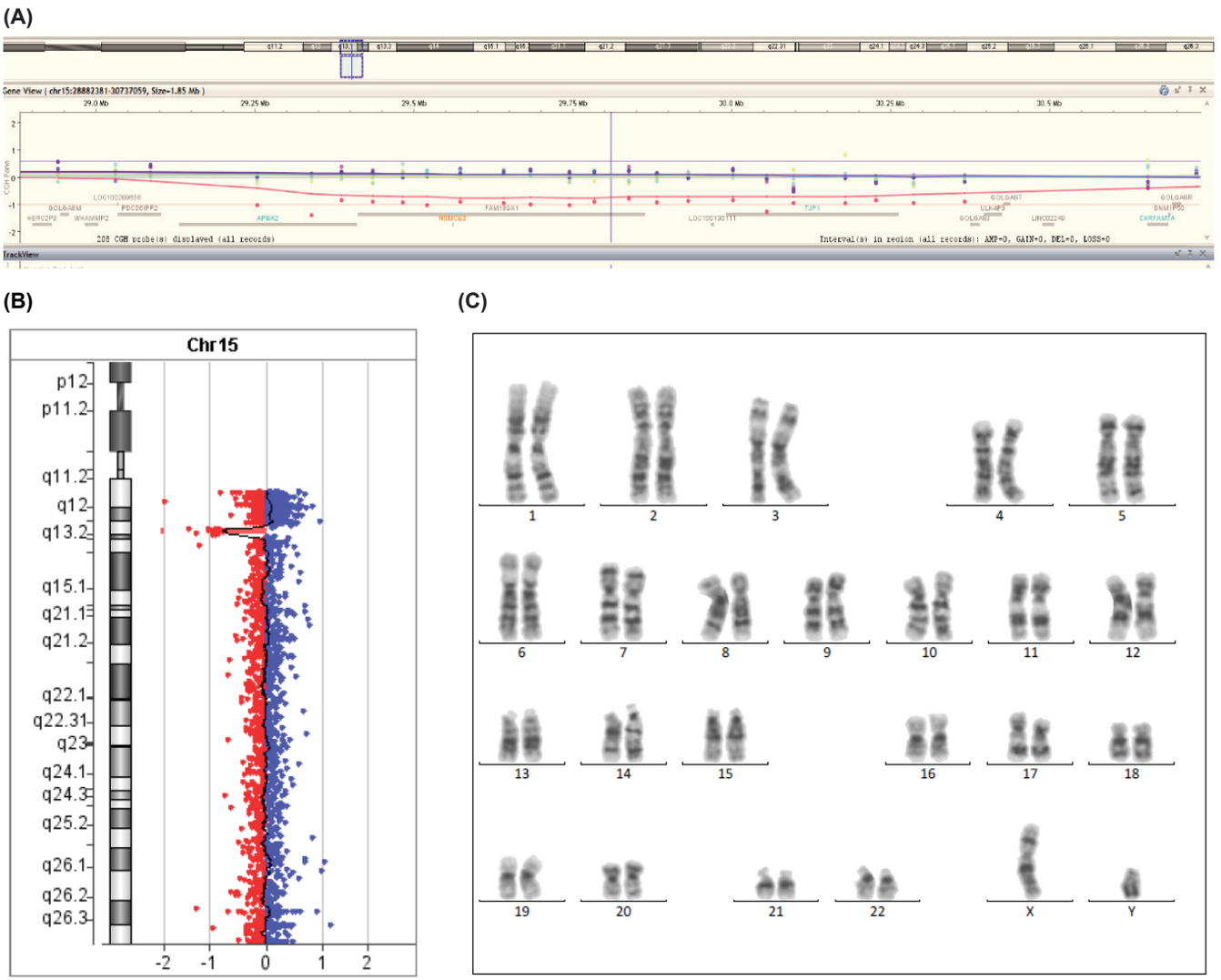

Fig. 2. Karyotype and array comparative genomic hybridisation analysis detects 1.1 Mb-deletion of the chromosome 15q13.1-q13.2 region containing 5 genes. (A) Comparison of 8 samples, **(B)** Deletion of chromosome 15, and **(C)** Normal foetus's karyotype.

Peripheral blood samples were taken from the foetus' parents and subjected to aCGH analysis, which did not identify any mutations. These results suggest that the foetus' chromosome with the microdeletion was not inherited from the parents. The pregnant woman reported having a regular menstrual cycle and a natural, uneventful pregnancy. She had no history of smoking, alcohol consumption, viral infections, or a family history of foetal anomalies. Additionally, she denied taking any oral medications during her pregnancy. Non-invasive prenatal testing was also conducted during the pregnancy, revealing a low risk. The pregnant woman and her family decided to terminate the pregnancy at 23 weeks of gestation. Unfortunately, we do not have the foetal pathology results after delivery because the family did not agree to an autopsy on the foetus.

3. Discussion

Genomic regions flanked by low-copy repeats (LCRs, or segmental duplications) with DNA sequence identity greater than 95-97% are prone to recurrent microdeletions, microduplications, and inversions mediated by non-allelic homologous recombination (NAHR) [6]. One of the most unstable regions in the human genome is the LCR-rich proximal region of chromosome 15 (15q11-q14), which is associated with various DNA copy-number variations (CNVs) such as deletions, duplications, inversions, translocations, and supernumerary inv dup(15) chromosomes [7]. The breakpoints of these rearrangements occur within complex sets of LCRs known as BP1 to BP6 [8].

Prader-Willi syndrome (PWS) and Angelman syndrome usually result from distinct parental-origin deletions that encompass the distal breakpoint BP3, along with proximal breakpoints BP1 or BP2 [8]. Another study on the UK Biobank revealed that the deletion of the 15q11.2 region spanning from BP1 to BP2, also known as the Burnside-Butler syndrome susceptibility locus, has been previously linked to various phenotypes, including developmental delay, autism, schizophrenia, and congenital cardiovascular malformation [9]. Supernumerary inv dup (15) chromosomes, also referred to as inverted duplications, are frequent rearrangements found in the 15q11-q13 region. These large inv dup (15) chromosomes are exclusively derived from the maternal side and have been observed in patients exhibiting facial dysmorphology, intellectual disability, severe epilepsy, and often autistic behaviour [10]. Duplications and inv dup (15) chromosomes commonly involve the breakpoints BP4 and BP5, which are characterised by duplicons consisting exclusively of LCR15 elements. These duplicons at BP4 and BP5 play a significant role in triplications and inv dup (15) chromosome rearrangements [7].

The consequence of microdeletion between BP3 and BP4 is rarely reported. The presence of shared clinical features among individuals with this deletion and the existence of genes involved in development and nervous system function within the deleted region suggest that this deletion potentially contributes to abnormal phenotypes in certain individuals [11].

This patient with congenital heart defect (CHD) was found to have a 1.1 Mb deletion of the chromosome 15q13.1-q13.2 region between BP3-BP4. A previous study in 2019 reported a case with two microdeletions on 15q13.2 and 15q13.3, corresponding to two intervals between BP3 and BP4, BP4 and BP5. The patient exhibited symptoms of microdeletion 15q13.3 syndrome and CHD, specifically a redundant mildly prolapsed mitral valve and mildly thickened cardiac muscle [12]. In addition, a study in 2020 described four members of a family with a microdeletion from BP3 to BP5, two of whom had CHD [13]. Furthermore, C. Lowther, et al. (2015) [14] proved that no significant differences were identified when analysing the clinical features of patients in groups with deletions in BP4-BP5, BP3-BP4, and BP3-BP5. Therefore, it can be hypothesised that the heart defect in the present case is caused by the 15q13.2 microdeletion situated between BP3 and BP4.

4. Conclusions

This deletion variant on the long arm of chromosome 15 identified by aCGH technique in this paper is the first reported case in the literature. This variant may be associated with severe heart defects. It contributes to the common data sources, providing clinicians and geneticists with additional basis for genetic counselling in general, and especially in cases of prenatal diagnosis of heart defects.

CRediT author statement

Thi Ha Vu: Performing the study, Data collection and analysis, Original draft preparation; Thi Hai Hoang, Thi Sim Nguyen, Khanh Dung Ho: Clinical diagnosis, Data collection; Thi Kim Phuong Doan: Conceiving and designing the study, Writing - Reviewing and Editing.

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Availability of data and materials

The data reported in this study are available upon request by contact with the corresponding author.

Ethics approval and consent to participate

This study was approved by the Ethics Review Committee of Hanoi Medical University Hospital affiliated with Hanoi Medical University (Approval No. 106/GCN-HDDDNCYSH_DHYHN, 24/06/2020). Written informed consent was obtained from the foetus's parents following a detailed description of the study's purpose. All experimental procedures described in this study were by international and national laws, regulations, and guidelines.

Consent for publication

The pregnant woman and her husband involved in this study agreed to publish related demographic and clinical features.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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