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A RARE CASE OF CHROMOSOME 17P13.3 MICRODUPLICATION: INSIGHTS INTO ITS DIAGNOSTIC JOURNEY.

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ABSTRACT

Chromosome 17p13.3 microduplication is a rare occurrence and as per literature only 40 cases have been reported so far. We report another such case and its prenatal diagnostic journey. The key learning point from this case is that non-invasive prenatal diagnostic screening (NIPS) has high sensitivity for detection of Trisomy 21, 18 and 13 alone. When multiple soft markers are present on ultrasound, invasive diagnostic testing should be preferred as other chromosomal abnormalities may be present.

KEYWORDS: Chromosome 17p13.3 duplication, PAFAH1B1 and YWHAE genes, Non-invasive prenatal diagnostic screening.

INTRODUCTION

Chromosome 17p13.3 is associated with microdeletion and microduplication syndromes because it has a high-density low copy repeats which renders it genetically unstable.[1]

At one hand the microdeletions within the 17p13.3 chromosome, due to either an insufficiency of the PAFAH1B1 gene or a heterozygous mutation in the PAFAH1B1 gene, has caused either Miller–Dieker lissencephaly syndrome, or isolated lissencephaly spectrum disorder respectively.[2] On the other hand, the overexpression of *PAFAH1B1 has* led to a recently described condition known as 17p13.3 microduplication syndrome with a wide range of phenotypic manifestations.[1,3]

According to literature, 17p 13.3 chromosome microduplication is associated with congenital malformations, hypotonia, and subtle hand and foot malformations.[4,5] Usually, the duplicated area is de novo and varies in size from 1.8 to 4.0 Mb[6,7], but smaller duplicated areas have also been reported.[8] The critical genes in microduplication include *PAFAH1B1*, *YWHAE*, and *CRK* and the clinical manifestations depend on these genes. The overexpression of the *PAFAH1B1* gene, encoding LIS1, affects brain development by causing migration defects. *YWHAE* encodes 14-3-3ε which affects neuronal network development and maturation, and *CRK* is known to interact with signal pathways involved in brain and limb development.[9]

There are two types of 17p13.3 microduplication syndrome: Class I and Class II. The phenotype of class I duplications, which involve YWHAE but not PAFAH1B1, includes modest facial and hand/foot dysmorphisms, autistic characteristics, and speech and movement delays.[1,8] The PAFAH1B1 gene is always present in class II duplications, which can also contain YWHAE and CRK. These duplications have a phenotype that includes microcephaly, growth restriction, developmental delay, and other brain abnormalities such minor cerebellar volume loss and corpus callosum hypoplasia.[1,8]

It has been found that on a prenatal ultrasound, where corpus callosum abnormalities are the hallmark feature, patients with 17p13.3 microdeletions have been easier to identify.[10] However, microduplication of the region is a random discovery during screening making the prenatal diagnosis of this condition a challenging procedure.[10] Furthermore, the genetic counselling is even more complicated as microduplication's phenotype expressivity and penetrance are not predicted.[11]

The first case of 17p13.3 microduplication was reported in 2009 and as per literature only 40 cases have been reported worldwide so far.[11] We present a unique case of prenatally diagnosed Class I 17p13.3 microduplication syndrome which showed subtle ultrasound features and confirmed by genetic testing.

CASE REPORT

A 31 year old primigravida was undergoing her routine antenatal check-ups. Her12 weeks scan reported a normal nuchal translucency (NT), an unossified nasal bone (NB) which was performed elsewhere. Her double marker test by Prisca software- reported low risk with PAPPA 0.36 MoM and Bhcg -0.3 MoM. In her next visit at our centre, at 18 weeks of gestation, her anomaly scan revealed a hypoplastic nasal bone, a single umbilical artery and mild unilateral renal pelvis dilatation. She was offered amniocentesis at this point of time but she opted for non-invasive prenatal screening (NIPS) for 5 common aneuploidies. The NIPS test result revealed low risk with a fetal fraction of 12 percent. Patient was called for rescan at 20-22 weeks for evaluation which revealed the following:

1. Intracranial structure- All axial views were normal on transabdominal scanning (Figure 1); The Cavum septum pellucidum appeared normal with length: width ratio 1.85 (Figure 2); Lateral Ventricular Vp- 6.2 mm (Figure 3) : In sagittal view the rostrum of corpus callosum was not visualized (Figure 4) with the corpus callosal length 17.2 mm (< 2.5th percentile) (Figure 5)
2. Unilateral hypoplastic nasal bone (1.9 mm in length) (Figure 6)
3. Unilateral renal pelvis dilation (AP diameter- 6 mm) (Figure 7)
4. Small Perimembranous ventricular septal defect. (Figure 8)
5. Single umbilical artery (Figure 9)

In view of the above findings the couple was counselled and amniocentesis was offered for whole exome sequencing along with testing of couple (Trio testing). The whole exome sequencing report revealed a de novo heterozygous duplication on chromosome 17p13.3 (Figure 10). The couple opted for termination of pregnancy. A male fetus of 450 gms was aborted with no external morphological abnormality. The couple refused for any autopsy or examination of fetus.

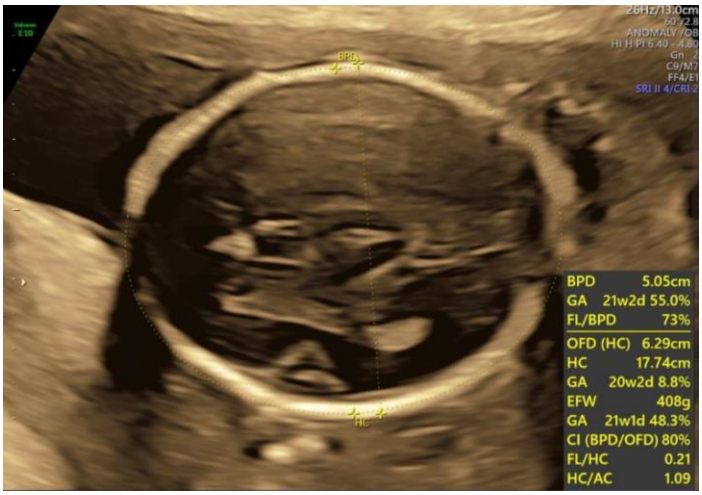


Figure 1: Axial view showing normal biparietal diameter.

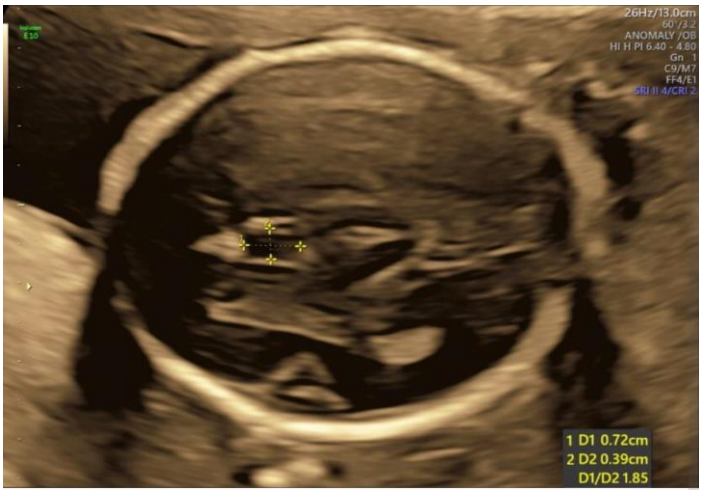


Figure 2: A normal cavum septum pellucidum normal with length: width ratio 1.85 on axial view.

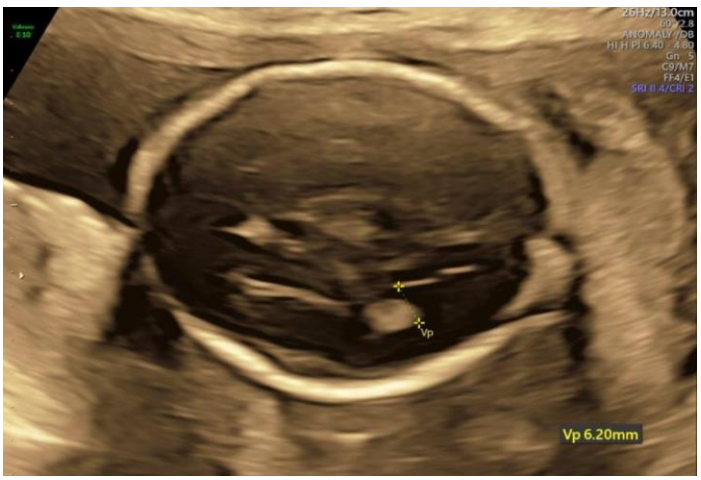


Figure 3: Lateral Ventricular measuring Vp- 6.2 mm.

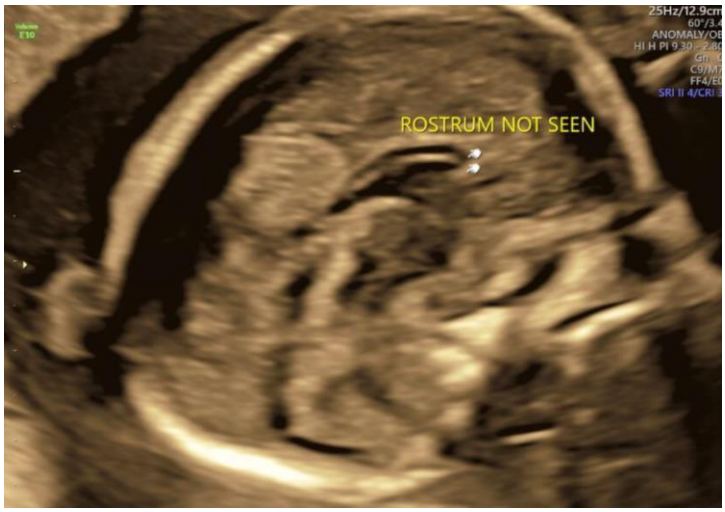


Figure 4: Sagittal view of brain suggestive of non-visualisation of rostrum.

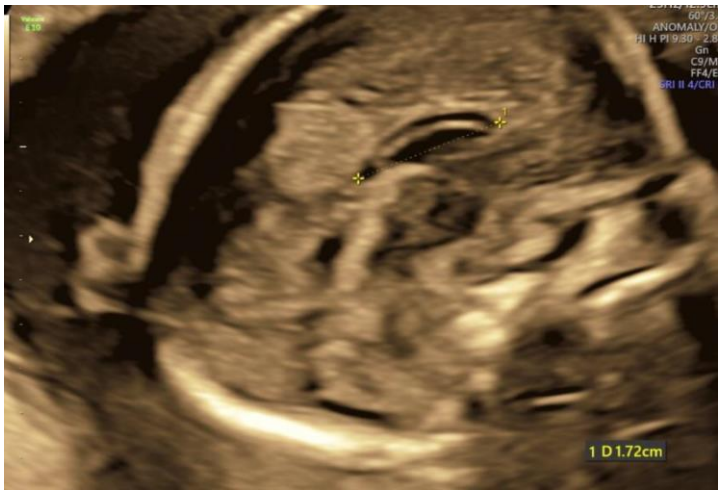


Figure 5: Sagittal view showing corpus callosal length 17.2 mm (< 2.5th percentile).

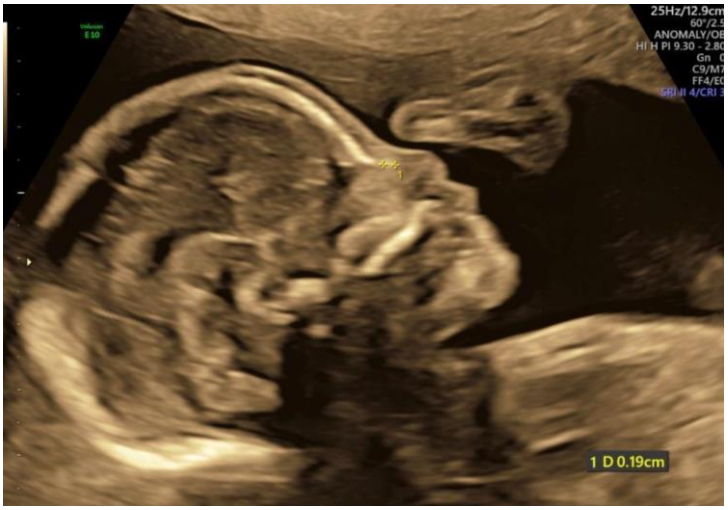


Figure 6: Unilateral hypoplastic nasal bone (1.9 mm in length).

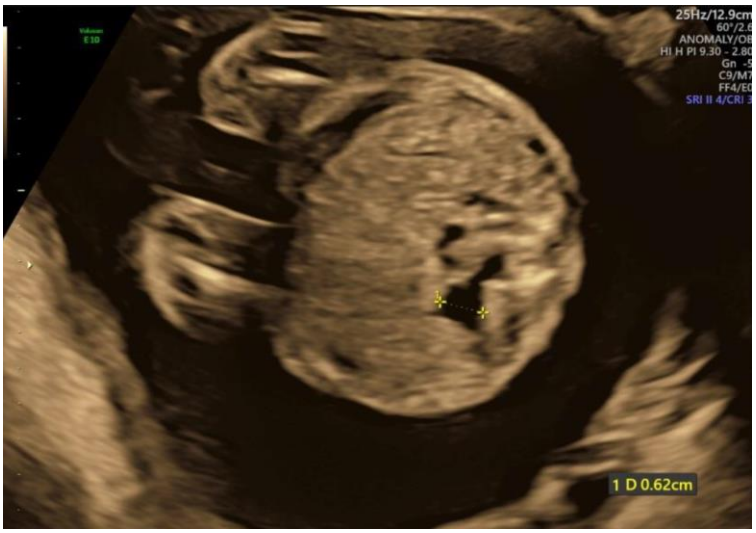


Figure 7: Unilateral renal pelvis dilation (AP diameter- 6 mm).

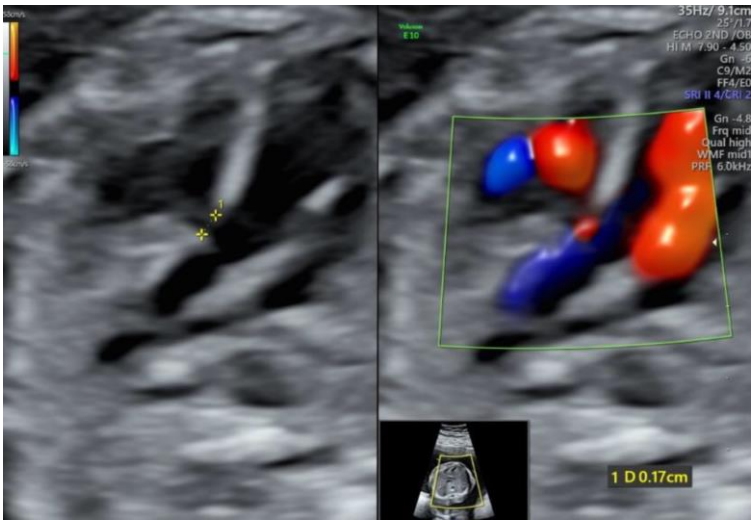


Figure 8: Small Perimembranous ventricular septal defect.

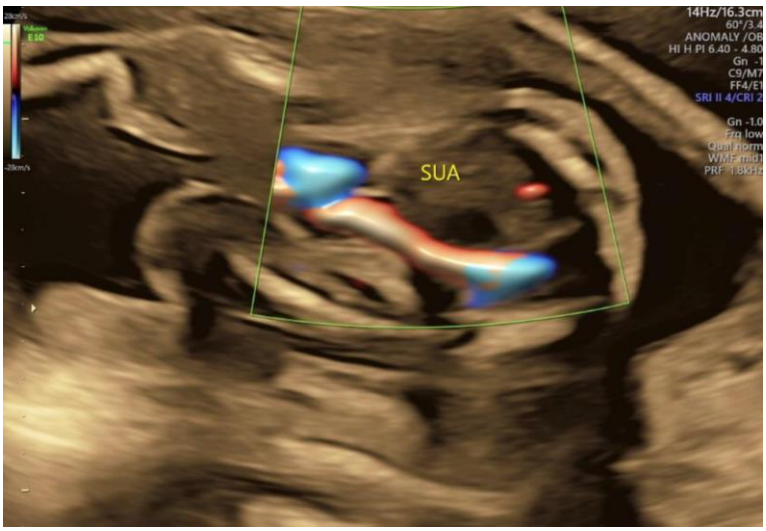
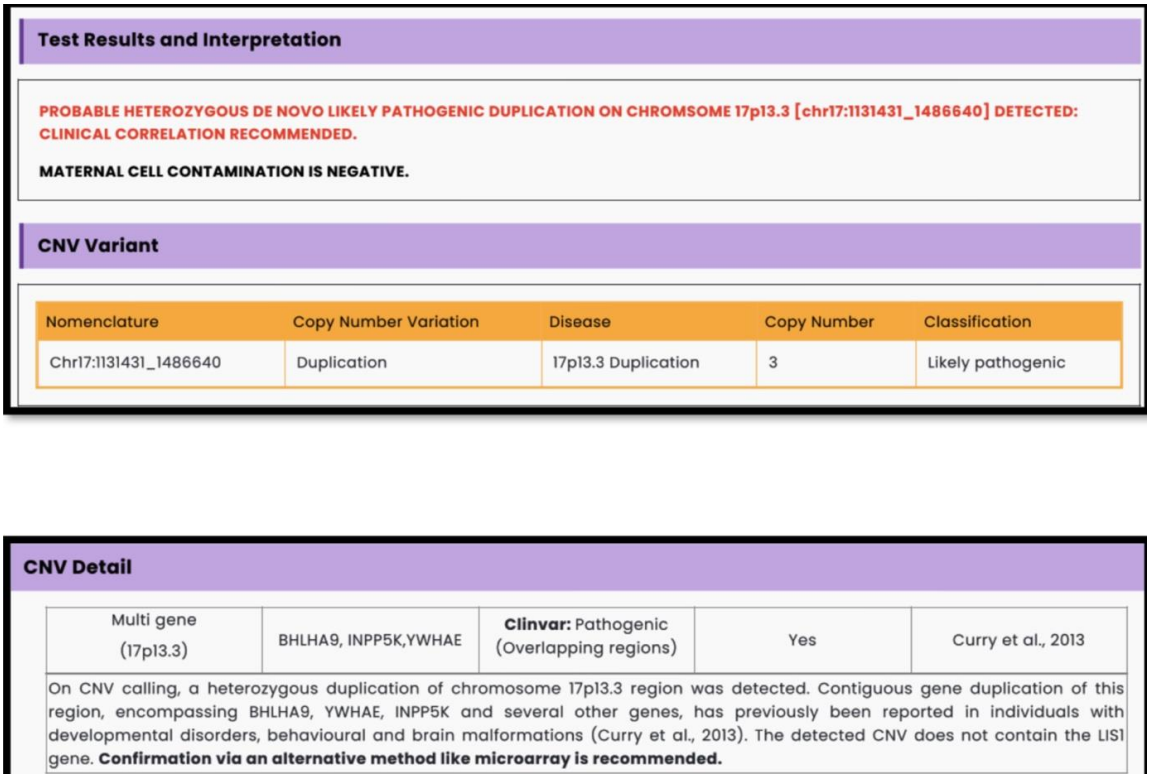


Figure 9: Single umbilical artery.



Test Results and Interpretation

PROBABLE HETEROZYGOUS DE NOVO LIKELY PATHOGENIC DUPLICATION ON CHROMSOME 17p13.3 [chr17:1131431_1486640] DETECTED: CLINICAL CORRELATION RECOMMENDED.

MATERNAL CELL CONTAMINATION IS NEGATIVE.

CNV Variant

Nomenclature	Copy Number Variation	Disease	Copy Number	Classification
Chr17:1131431_1486640	Duplication	17p13.3 Duplication	3	Likely pathogenic

CNV Detail

Multi gene (17p13.3)	BHLHA9, INPP5K,YWHAE	**Clinvar:** Pathogenic (Overlapping regions)	Yes	Curry et al., 2013

On CNV calling, a heterozygous duplication of chromosome 17p13.3 region was detected. Contiguous gene duplication of this region, encompassing BHLHA9, YWHAE, INPP5K and several other genes, has previously been reported in individuals with developmental disorders, behavioural and brain malformations (Curry et al., 2013). The detected CNV does not contain the LIS1 gene. **Confirmation via an alternative method like microarray is recommended.**

Figure 10: The test result of genetic testing showing 17p13. 3 duplication.

DISCUSSION

Chromosome 17p13.3 is a gene dense region which is associated with the well-known Miller-Dieker syndrome when deletion occurs. The clinical characteristics of microdeletion syndromes are lissencephaly (pachygyria and incomplete or absent gyration of the cerebrum), microcephaly, hypotonia, dysmorphic facial features (narrow forehead, downward-slanting palpebral fissures, or small nose and chin), cardiac malformations, growth retardation, and mental deficiency with seizures and EEG abnormalities.[1,3] A recently described duplication syndrome involving this region has been associated with intellectual impairment, autism, and brain MRI abnormalities. Bruno L.D. et al. [3], reported that intrauterine growth retardation, developmental delay, special facial features, and structural brain abnormalities are some of the features common to both deletion and duplication syndromes, but behavioural problems and autistic spectrum disorders are observed only in duplications.

In our case the patient had an initial normal NT scan and a low-risk double marker report. Her anomaly scan at 18 weeks revealed more than 2 soft markers, so she was offered invasive testing, but the patient opted for a NIPS instead. Even though the NIPS test was low risk, later in a 22 week scan multiple anomalies were detected. This highlights that there are limitations of NIPS in screening for chromosomal abnormality. NIPS has high sensitivity for detection of Trisomy 21, 18 and 13 alone. The main educational insight here is that when multiple soft markers are seen, invasive diagnostic testing particularly for microarray, should be preferred as other chromosomal abnormalities may be present. Amongst the corpus callosal abnormalities – partial agenesis of the corpus callosum and mild, nonspecific thinning of the corpus callosum has been reported mainly with Class II 17p13.3 microduplication syndrome. In our case the rostrum of corpus callosum was not visualized with the corpus callosal length 17.2 mm (< 2.5th percentile) and the genetic testing revealed it to be Class I microduplication. The key learning point here is that corpus callosal dysgenesis or partial agenesis can be diagnosed reliably only after 20 weeks, hence anomaly scans should be targeted in the 20-22

week window period. The prenatal ultrasound imaging of 17p13.3 microduplication syndrome has also reported single umbilical artery and renal pelvis dilation which was seen in our case as well.

CONCLUSION

Our case raises awareness for a rare genetic 17p13.3 microduplication syndrome. It underscores the diagnostic limitations of non-invasive prenatal screening (NIPS), particularly in detecting rare chromosomal abnormalities such as 17p13.3 microduplication. Despite a low-risk NIPS result, multiple anomalies were later identified, highlighting the importance of opting for invasive testing like chromosomal microarray when multiple soft markers are present. Additionally, the case reinforces that structural abnormalities like corpus callosal dysgenesis can be more accurately diagnosed after 20 weeks gestation. Therefore, a targeted anomaly scan between 20–22 weeks, combined with appropriate genetic testing, is crucial for accurate prenatal diagnosis and counselling.

Conflict of interest: The authors have no conflict of interest relevant to this article.

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